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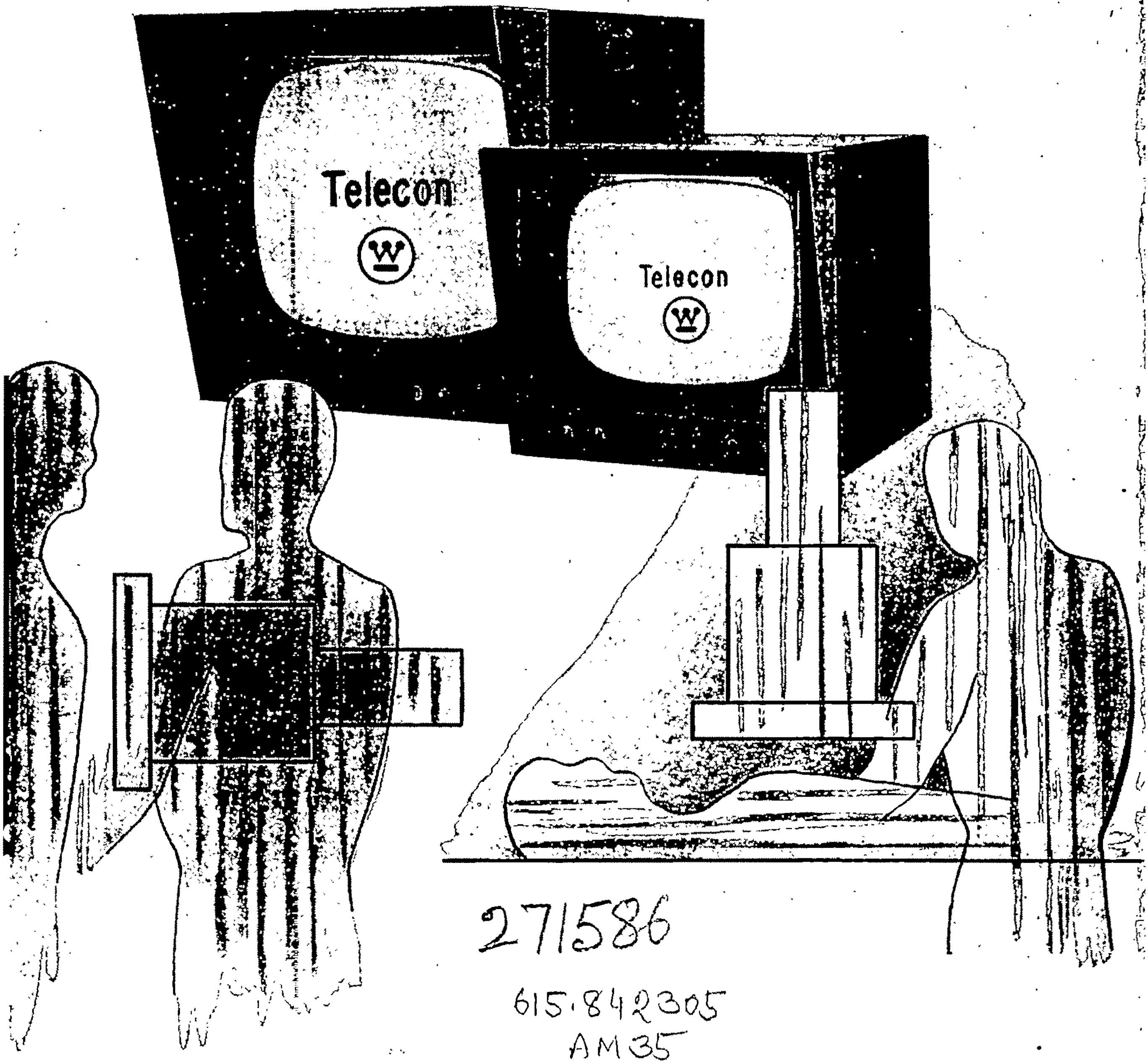

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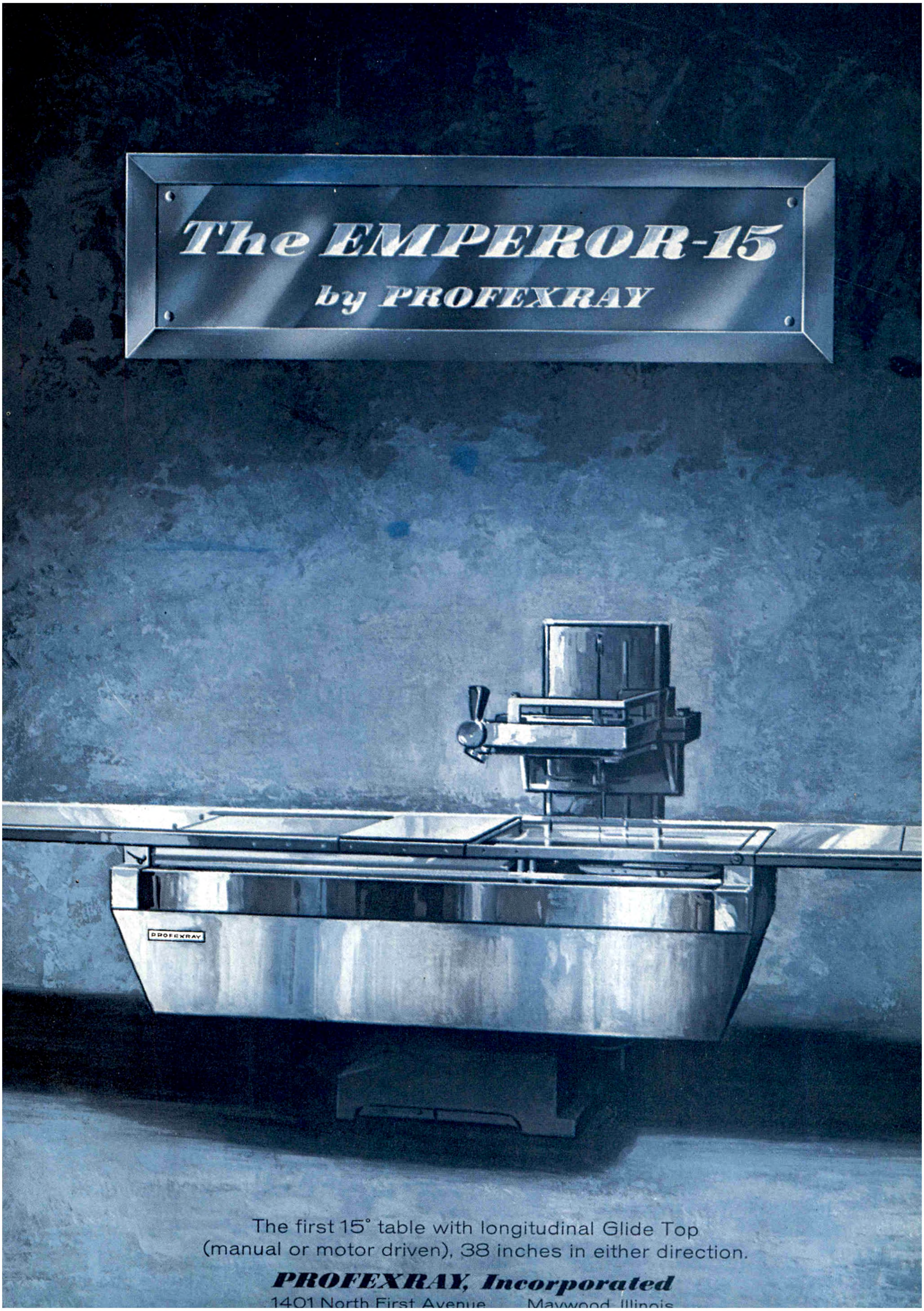

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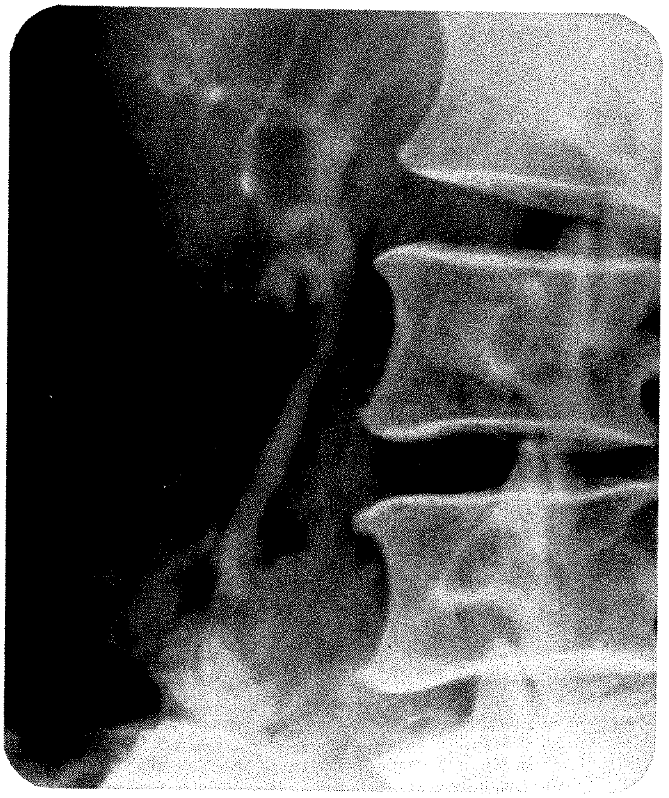

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References: (1) Cohn, E. M.: Am. J. Gastroenterol. *35*:115 (Feb.) 1961. (2) Jones, M.D., et al.: J. Pediat. *53*:172 (Aug.) 1958. (3) Machella, T. E.: Gastroenterology *34*:1050 (June) 1958. (4) Orloff, T. L.: Am. J. Roentgenol. *80*:618 (Oct.) 1958. (5) Johnson, G., Jr., et al.: Ann. Surg. *152*:91 (July) 1960. (6) McClenahan, J. L.: Pennsylvania M. J. *62*:188 (Feb.) 1959.

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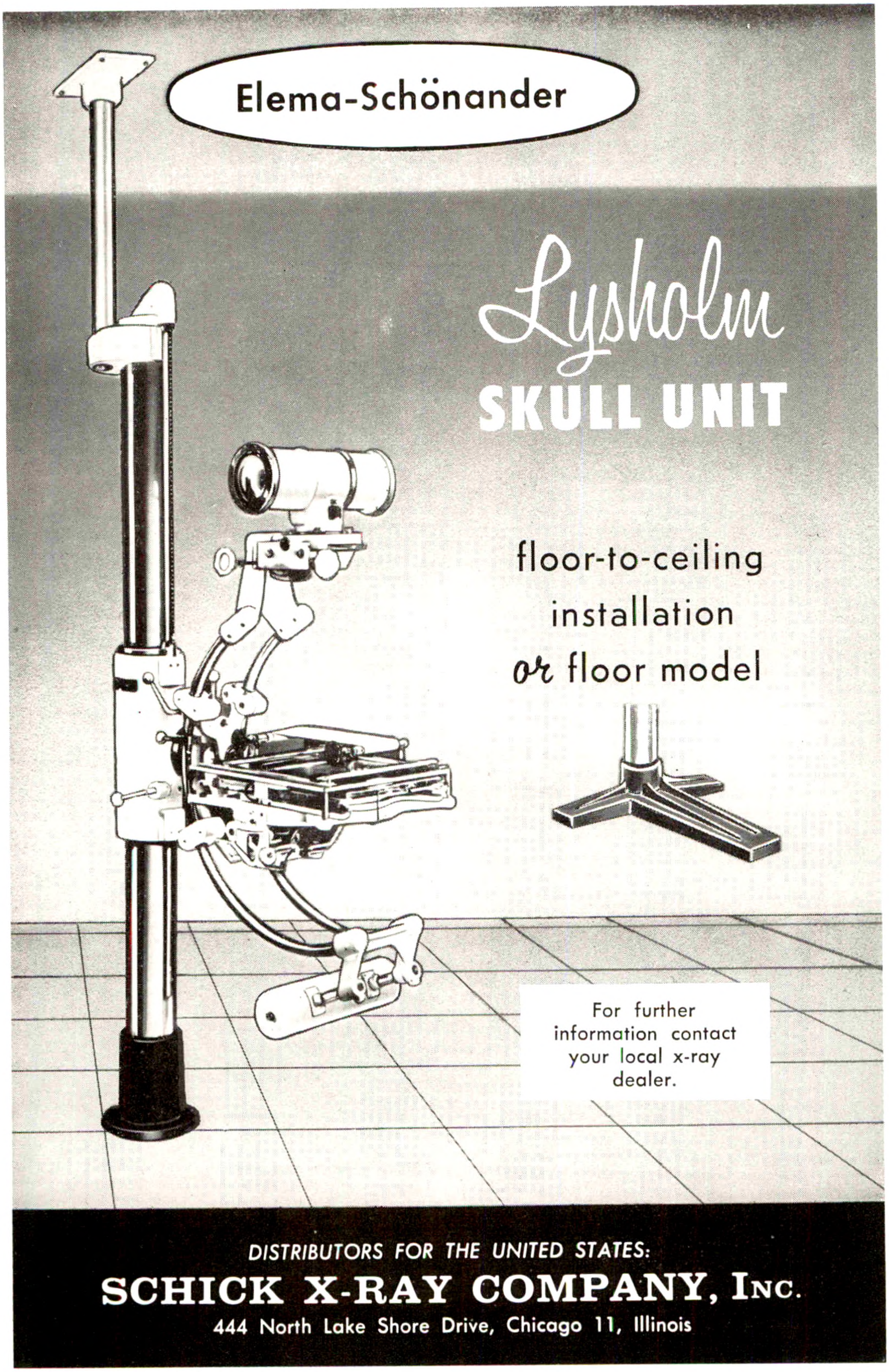

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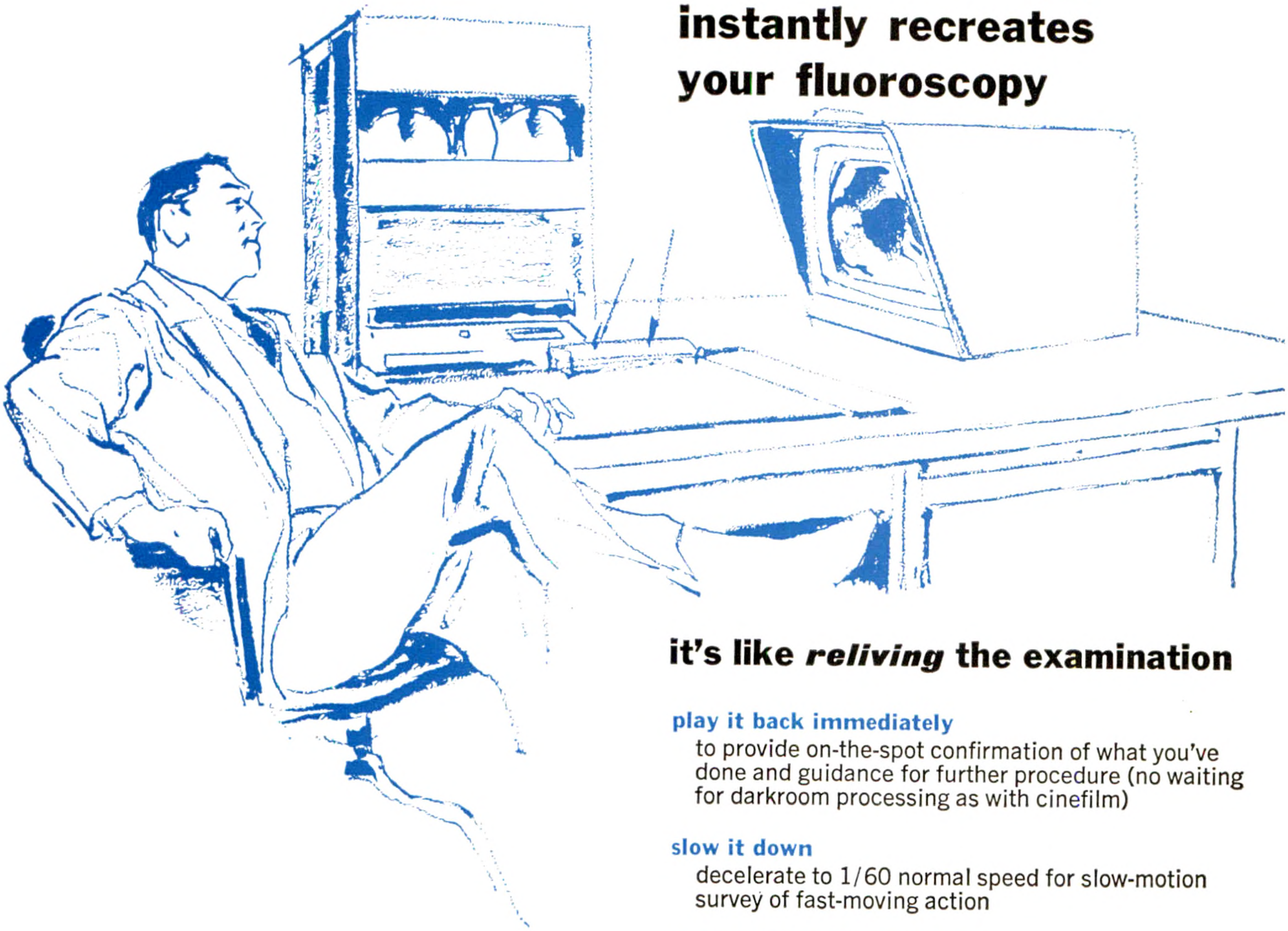

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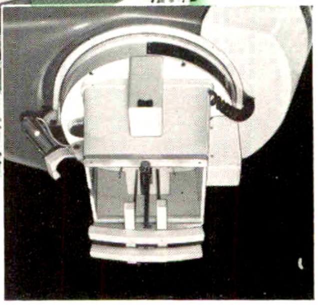

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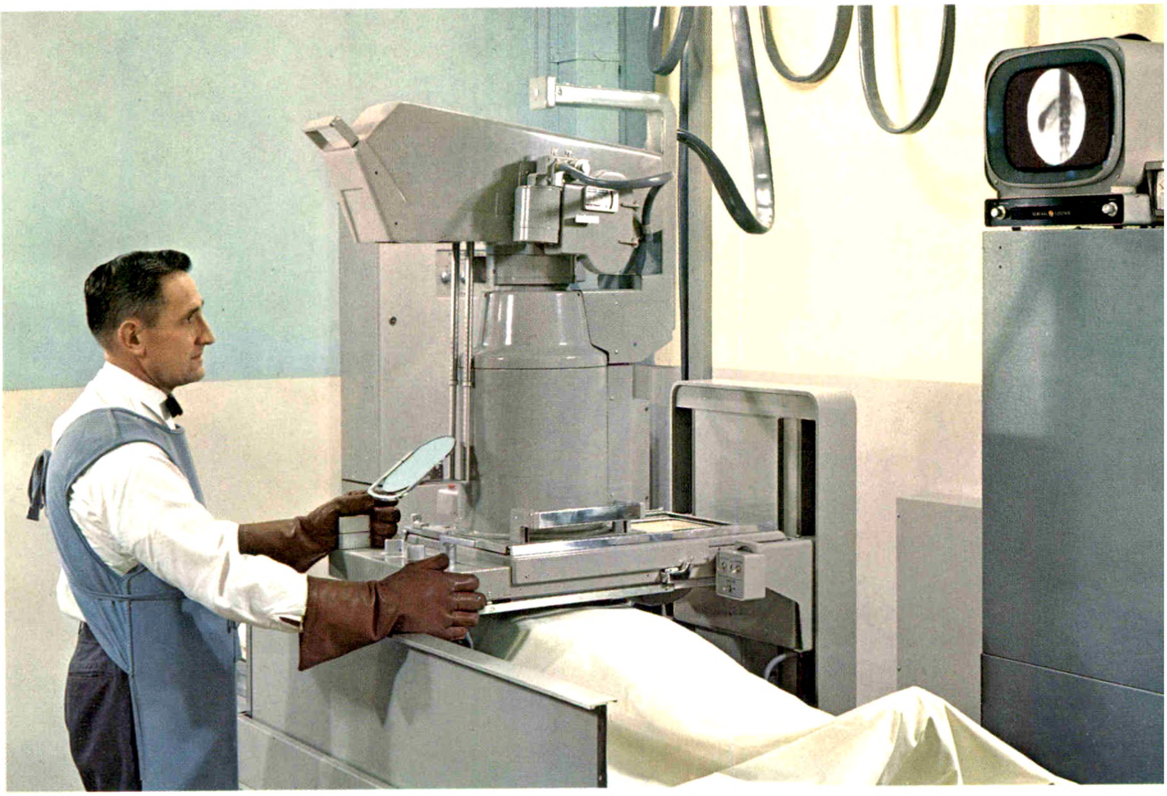

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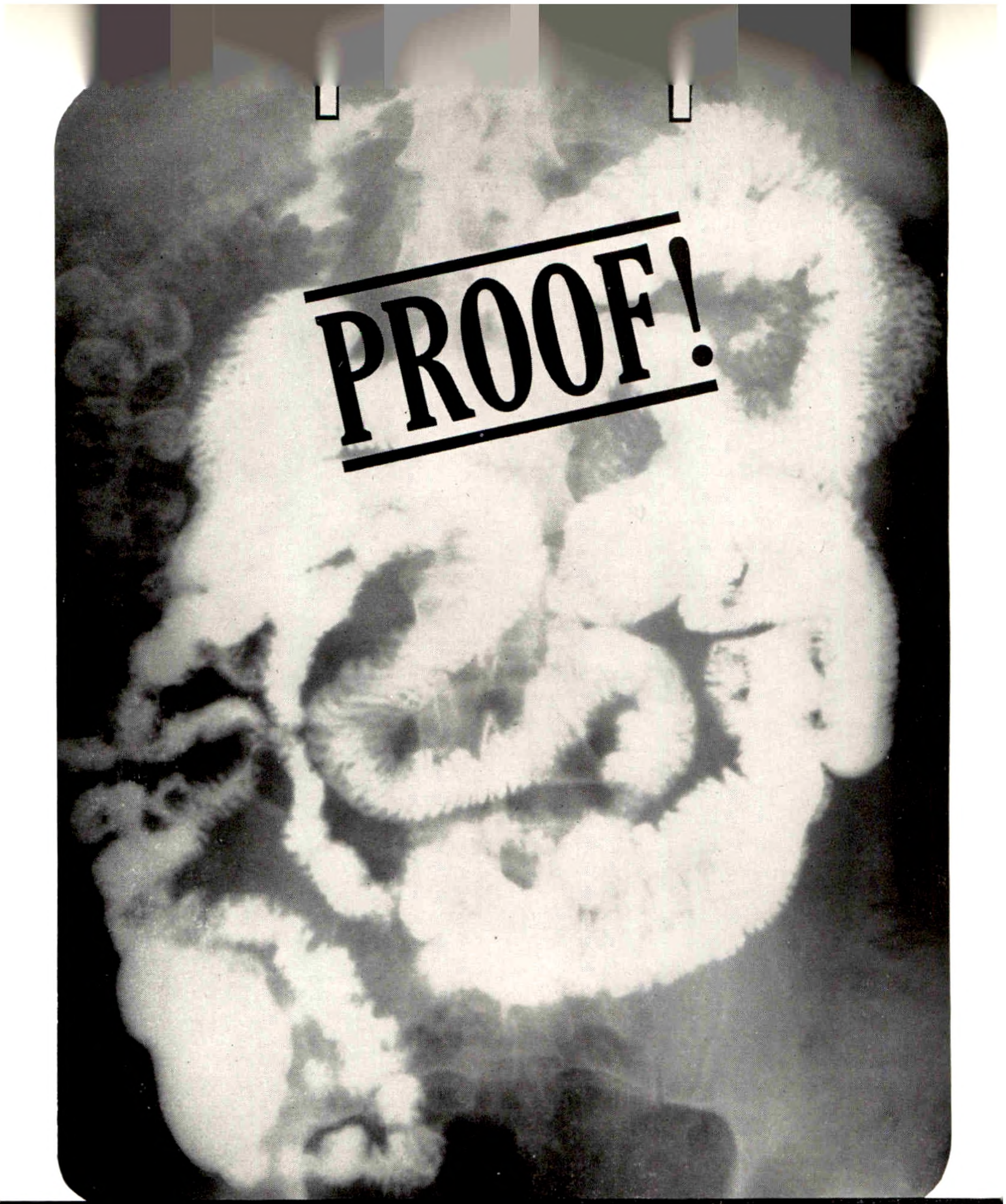

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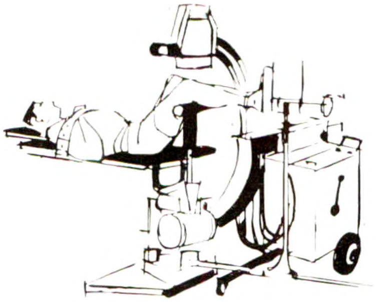

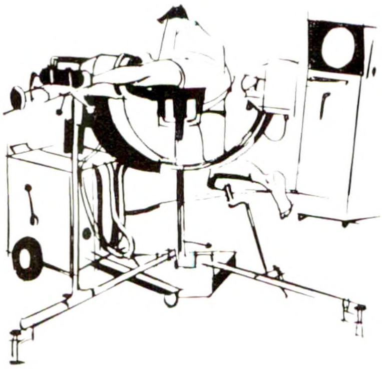

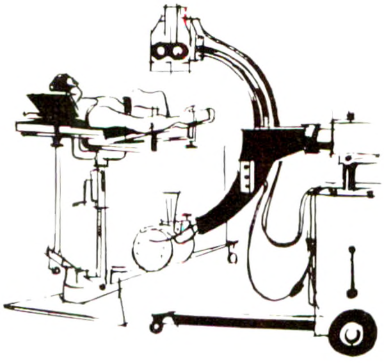

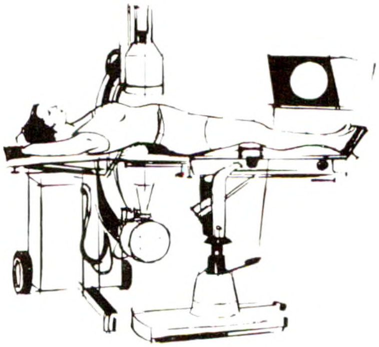

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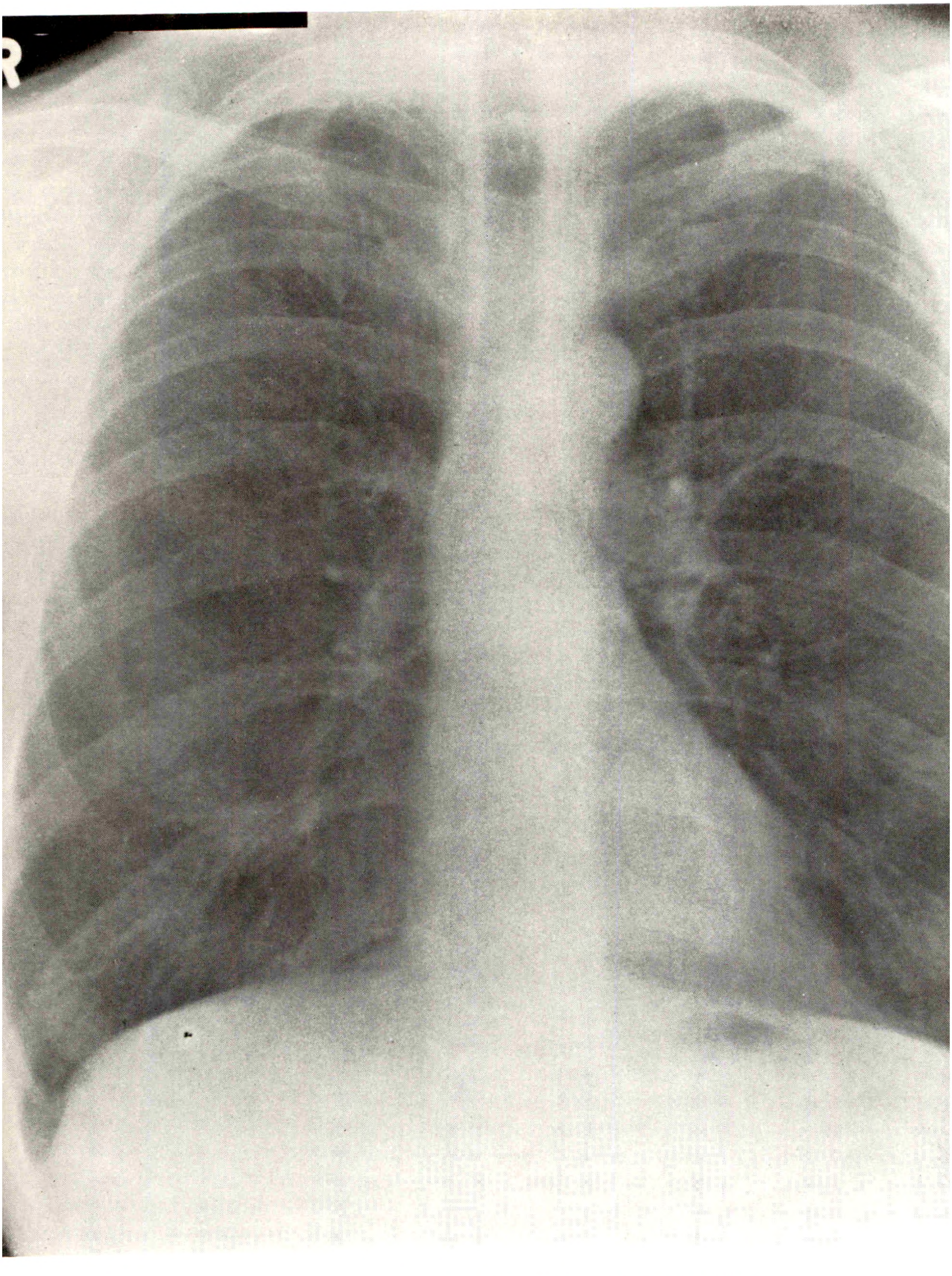

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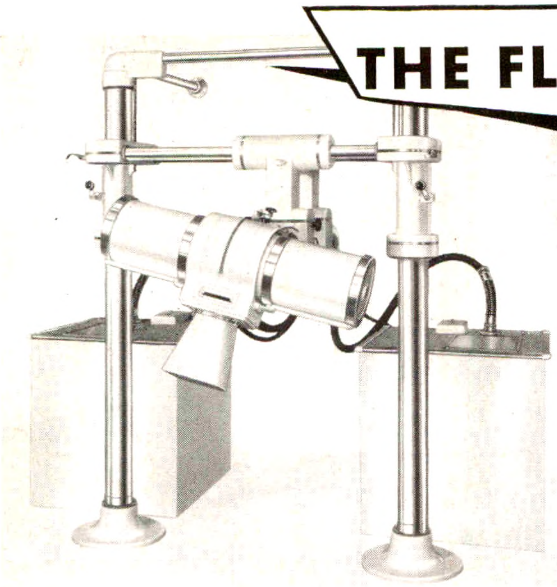

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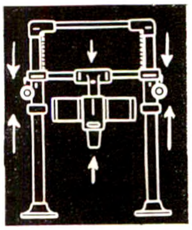
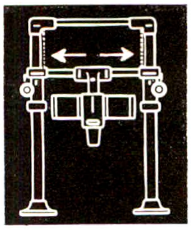
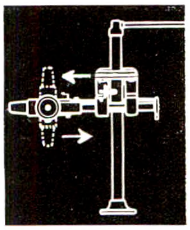


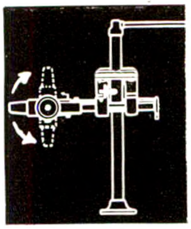
SAVE TIME—Move Flexray tube from side to side, 29″ cross travel in less than 4 seconds. Because the Transformer is not in the tube housing, Flexray weighs only a fraction of self-contained units—moves swiftly with fingertip pressure.



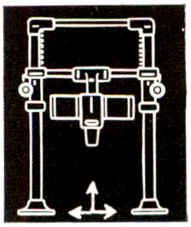
SAVE TIME—15″ in-and-out movement speeds your work. Vernier controls for precision adjustment. Compare the advantages of Flexray linear motion with the circular motion of self-contained apparatus.



SAVE TIME—The Flexray tube housing rotates a full 90° in either direction from horizontal. The x-ray tube, in fixed alignment with treatment cone, rotates a full 210° about its long axis. Needle bearings make movement easy. Retains fixed position automatically.



SAVE TIME—The Flexray Gantry type tube stand enables you to position the patient between or in front of the uprights which are obstruction free. You can place the patient exactly where desired, thus saving valuable time.



Standard X-RAY COMPANY

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An important new source for premium-quality X-ray film and chemicals

Cenco, world's largest supplier of scientific instruments for education, research, health, and industry has joined hands with Ferrania, giant of the European film industry, to bring you exceptionally high quality X-ray film and chemicals. Ferrania produces these materials; Cenco X-Ray Company distributes and guarantees them in the United States.

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Ferrania film is one of the world's most highly regarded and widely used X-ray films. For 35 years it has been produced to exacting standards of uniformity and performance. Absolute consistency, minimal base fog, high speed, excellent resolution, wide latitude and high contrast are characteristic of each sheet of Ferrania film.

Ferrania, a part of the Fiat group, is one of the world's largest manufacturers of photographic film. It is headquartered in Milan, Italy, and has plants at Milan and Ferrania, Italy, and at Buenos Aires, Argentina.

Cenco Instruments Corporation, a major supplier of scientific instruments and supplies to the American scientific community since 1889, has established a completely new division, Cenco X-Ray Company, to distribute Ferrania products in the U. S.

The new team of Cenco and Ferrania brings you radiographic materials of unmatched value—quality of the first order with economy. Close cooperation between Cenco and Ferrania has resulted in X-ray film and chemicals that meet the most exacting needs of American radiologists. Your Ferrania dealer will be calling on you soon to tell you more.

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Halsey Safelights

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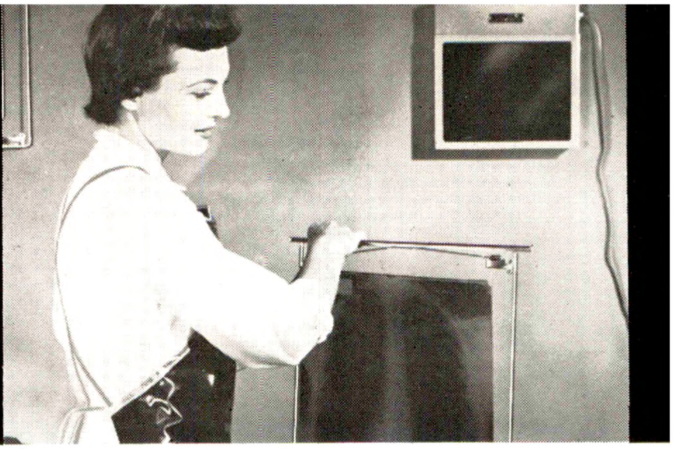


No. 275-SL-S

COMBOLITE DELUXE

Stainless steel — only 3¼″ deep

Compact combination of 8 x 10″ safelight and 4 x 10″ wet-film viewer — with built-in safeguard to prevent accidental lighting of viewer section. **No. 275-SL-S**

COMBOLITE

Same as above, but fabricated of cold-rolled steel with baked-on Silvergray finish. **No. 275-SL**

MONOLITE DELUXE

Stainless steel — only 3¼″ deep

Extra-thin 8 x 10″ safelight . . . valuable in tight quarters; can be mounted over the developing tank, yet will not be in the way of film hangers. **No. 272-SL-S**

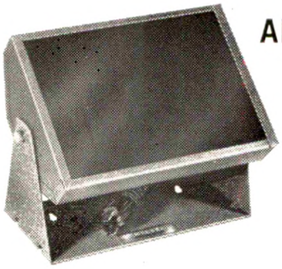
MONOLITE

Same as above, but with steel housing finished in baked-on Silvergray. **No. 272-SL**

MONOLITE JR.

A 5 x 7″ version of the Monolite. **No. 279-SL**

No. 272-SL-S



ADJUSTABLE SAFELIGHT

Tilts to any desired angle to throw light right where it is needed.
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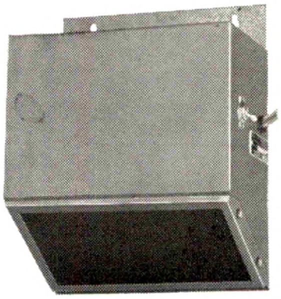
ANGL-LITE

An economical angulated safelight designed to provide a good spread of light over the bench or tank. **No. 276-SL**



Also: other combination safelight-viewer models; circular safelights; and 10 x 12″ wall and ceiling hung models.

Through your dealer
Write for detailed literature

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CHICAGO: 7321 Monticello Ave., Skokie, Illinois

Parallax impairs the sharpness of your image

CRONAR* polyester film base reduces parallax by bringing the two layers of emulsion closer together (.007" vs .008" for acetate base). Thus you get a sharper roentgenographic image to read. CRONAR can be made thinner because this polyester is far stronger and more stable than acetate.

CRONAR base has other advantages for radiology. The polyester has high optical clarity. It transmits more light to give you a brighter picture.

This unique material is almost impervious to water and processing solutions, too. Films don't go limp in processing units—they transport better, with less chance of jamming your processor.

You'll see (and feel and hear!) the difference, when you snap a CRONAR base film up on the viewbox.

*Du Pont's registered trademark for its polyester film base

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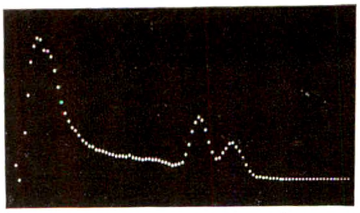

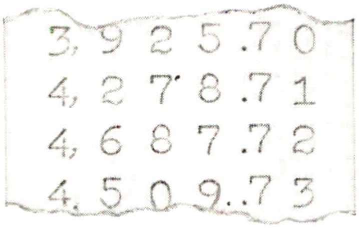

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4,278.71
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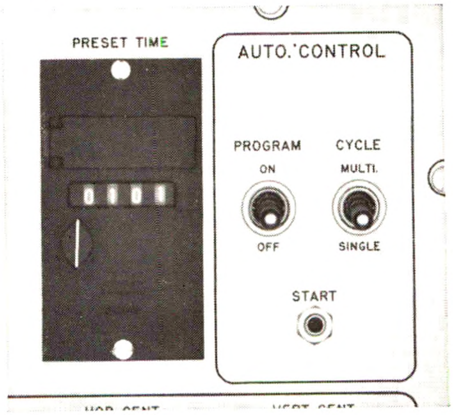
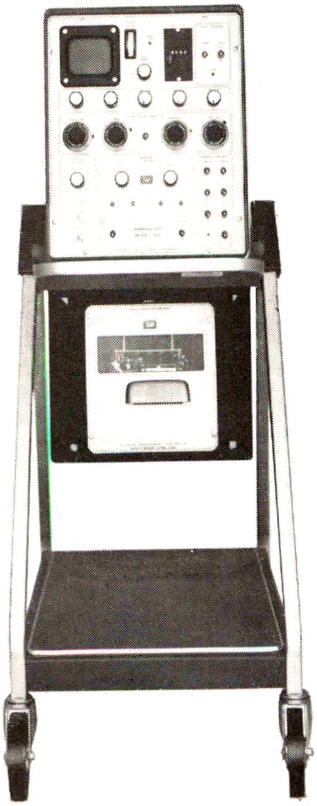


automatically — in a fraction of the time required by a scanning spectrometer



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PULSE HEIGHT ANALYZER

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including digital printer

The Gammascope provides extremely fast and accurate analysis of whole body counts, thyroid uptake studies and virtually all other medical and biological applications of nuclear radiation. Yet the price of the Gammascope, including a digital printer, is comparable to that of most single-channel scanning spectrometers.

After initial set-up and calibration the Gammascope will automatically accumulate 100 channels of data — no manual or electrical scanners are needed. The entire analysis operation takes a small fraction of the time that would be required by a single-channel spectrometer.

The build-up of a radiation energy spectrum in the magnetic core memory may be observed on the built-in cathode ray tube display. After accumulation is complete, stored data is read out in digital form — far more accurately than an analog plot made with a strip chart recorder.

The Gammascope combines both single and multi-channel capabilities. A variable "window" (restricted energy range) permits selection of any area of the spectrum, for intensification and study. The primary energy peak can be isolated for count summation by an auxiliary scaler.

All the circuits including high voltage supply, linear amplifier, preset live timer, live time meter, add/subtract logic and static or dynamic display are built into the single, highly portable unit. This essentially replaces an entire rack of equipment that would make up a complete single-channel scanning spectrometer.

Complete operating data and applications information are available from local TMC offices or from Technical Measurement Corporation, 441 Washington Avenue, North Haven, Connecticut. 203 239-2501.

TMC

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Dependability

In the key decisions of diagnosis, you must rely professionally on radiographs in which you can place full confidence. *Speed* that reduces risk of involuntary movement on the part of the subject, that sharpens detail; *gradation* that unfailingly produces a wide range of opacities with correct contrast; these properties are vital to consistent quality and to avoid wasteful rescheduling of procedures. Other important factors are fineness of grain and the utmost in reproducibility. All are characteristic of Ilford Red Seal X-ray Film, crafted in the finest British tradition. Each package bearing the Ilford Red Seal label is the product of continuing research and highest scientific standards. Red Seal X-ray Film in all standard sizes and bulk pack, together with Ilford Chemicals and Intensifying Screens, are available through your regular dealer.

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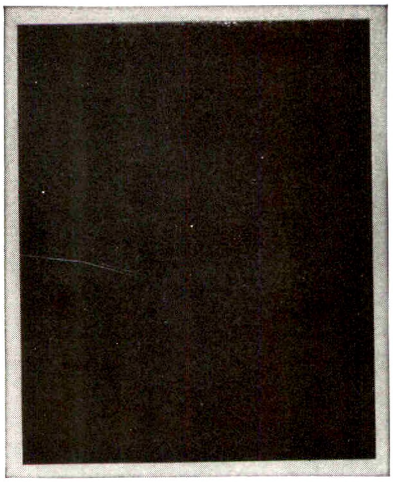
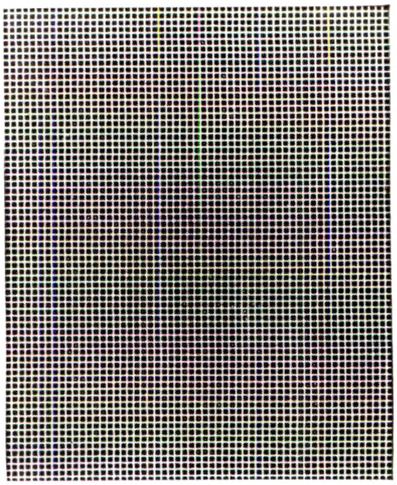
HOW MUCH HAVE YOU LOST--

due to lack of proper cassette contact?



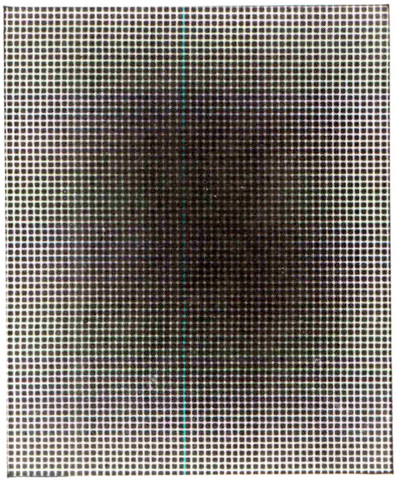
A—CASSETTE CONTACT TESTING GRID

B—FILM SHOWING PROPER CONTACT



Have you spent thousands of dollars for high power equipment and fine focus tubes in order to produce the sharpest possible detail—only to be disappointed due to lack of cassette contact?

Do you test your cassettes for contact each time you clean your screens?



C—FILM SHOWING IMPROPER CONTACT

A Buck Cassette Contact-testing Grid consists of two sheets of Bakelite, between which is permanently mounted a single layer of copper screen of suitable size, weight and mesh to fit a 14 x 17 or smaller size cassette.

To test a cassette for contact, place cassette, containing unexposed x-ray film, on x-ray table with Bakelite or front side of cassette UP; then place grid on top of cassette. Place tube target over center of grid—grid to target distance 24 inches. Give MA exposure equivalent to that required for a hand and process film as usual.

One Grid for all sizes of Cassettes 14 x 17 and smaller

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CLYSODRAST used as an enema is an effective means of cleansing and preparing the colon for radiologic examination.

The effective agent in CLYSODRAST is a nonirritant which stimulates the musculature to contract. The Tannic Acid in CLYSODRAST has a favorable influence on the deposition of Barium Sulfate on the mucosa and aids in preparation of the colon.

CLYSODRAST 4,4′ (DIACETOXYDIPHENYL)-(PYRIDYL-2)-METHANE AND TANNIC ACID N.F.

Note: Cramping, weakness, nausea and fainting occur more often with this product than with less effective enemas. It should be employed with caution where colitis is known to exist. Warning: Use with great care in patients where old age, debility, cardiovascular or other diseases are present.

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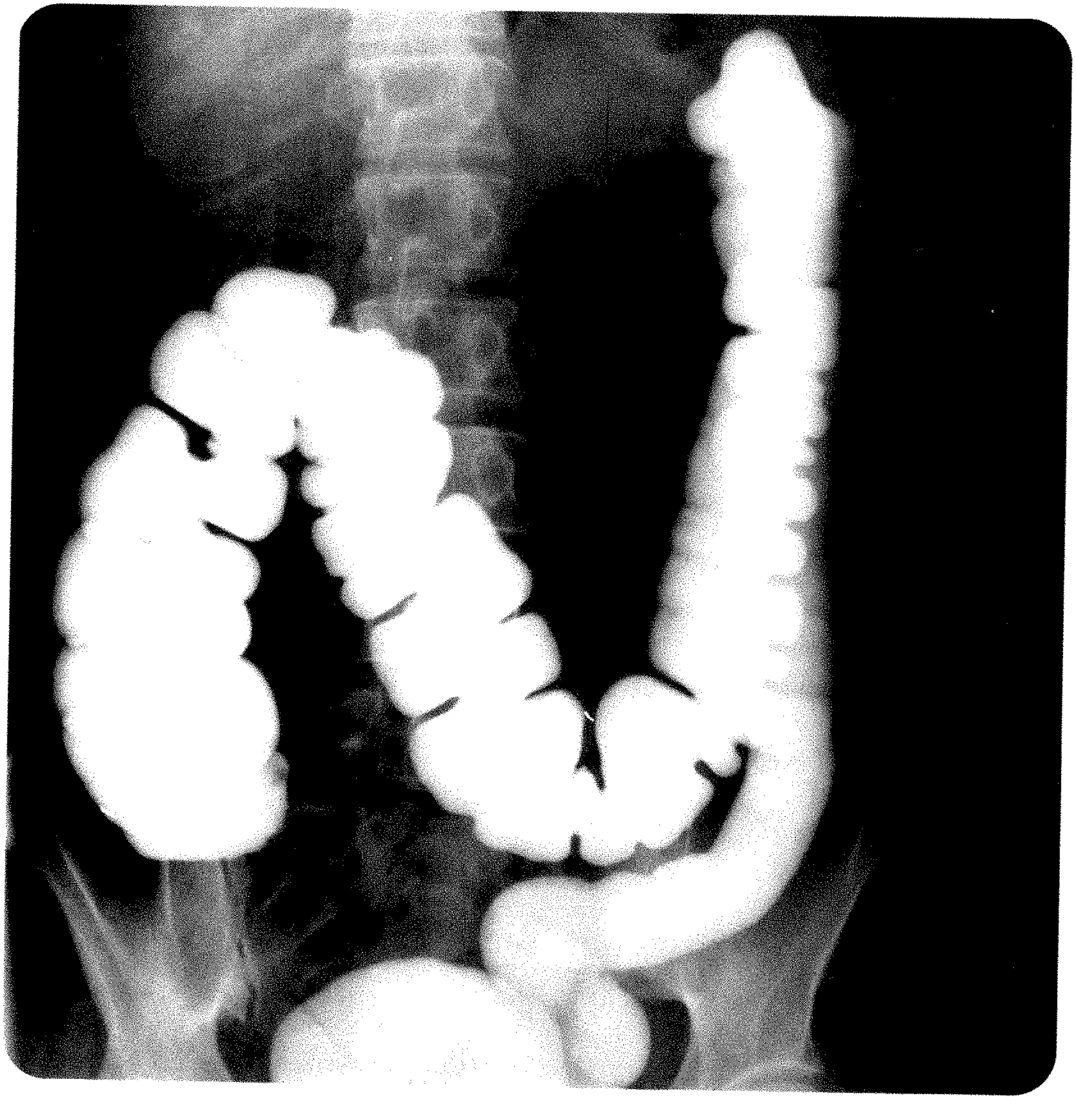
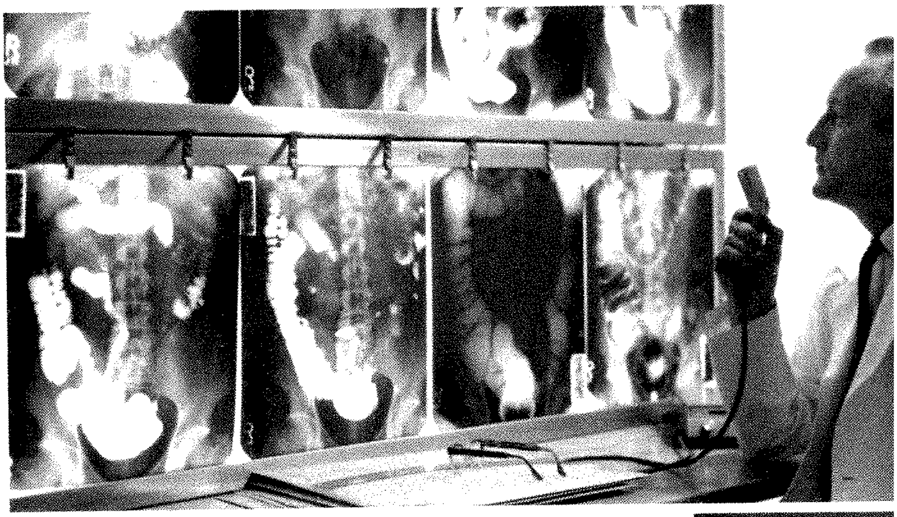


See the difference...



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PROCESSED IN LIQUAMAT® CHEMICALS

Ansco High Speed Film provides radiographs unsurpassed for sharpness of detail, contrast and variation in density...the things so important to confident diagnosis. Truly, these fine films give you radiographs with a difference you can see—clearly.

Of course, processing is also extremely important to radiographic quality. And for processing High Speed Film in automatic roller processors, tests show new Liquamat excels in all important processing characteristics.

Yes, you can depend on Ansco High Speed Film and Liquamat Chemicals to provide radiographs with a quality difference you can see. Contact your Ansco X-ray Representative for a demonstration and see for yourself.

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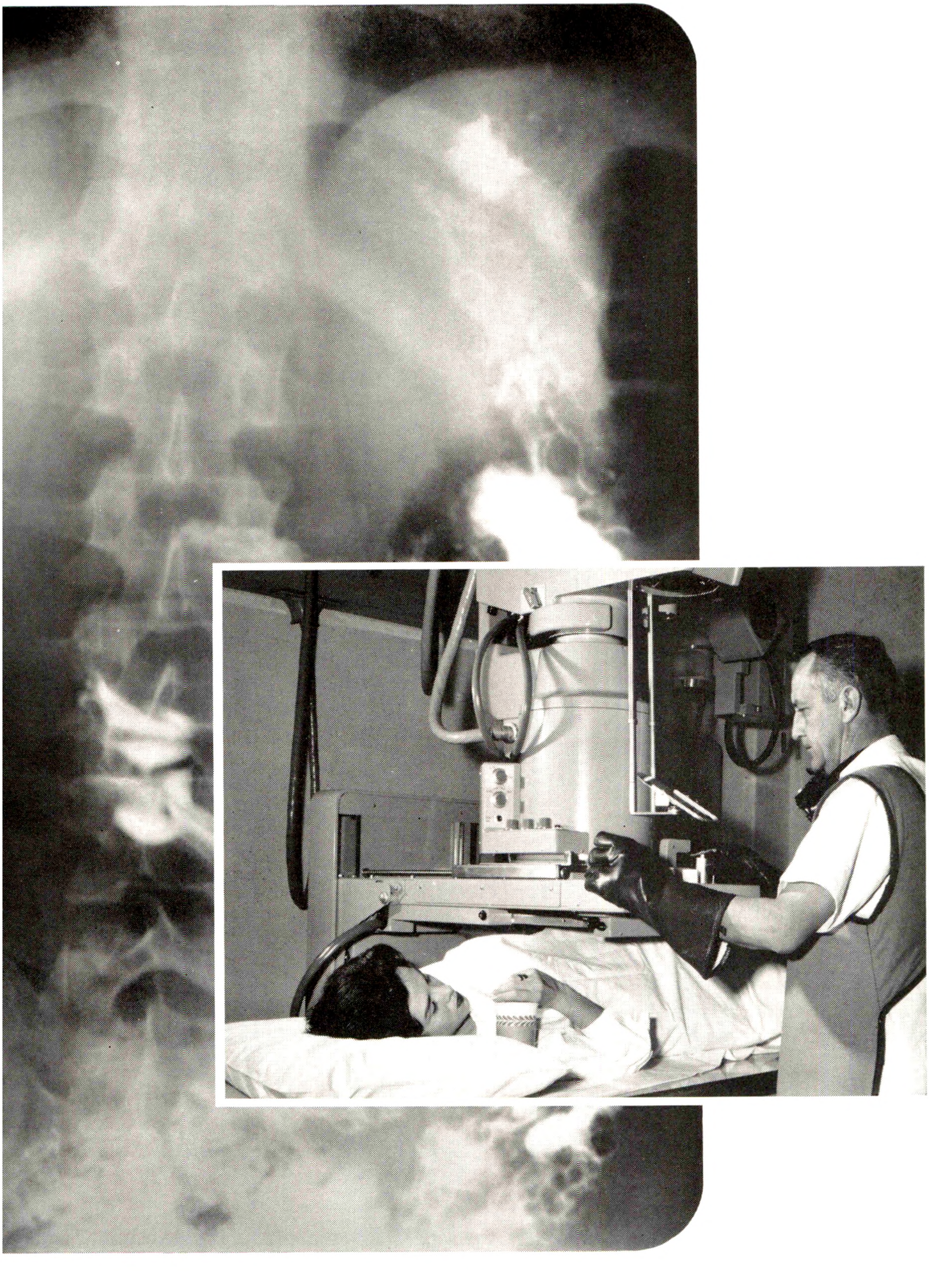

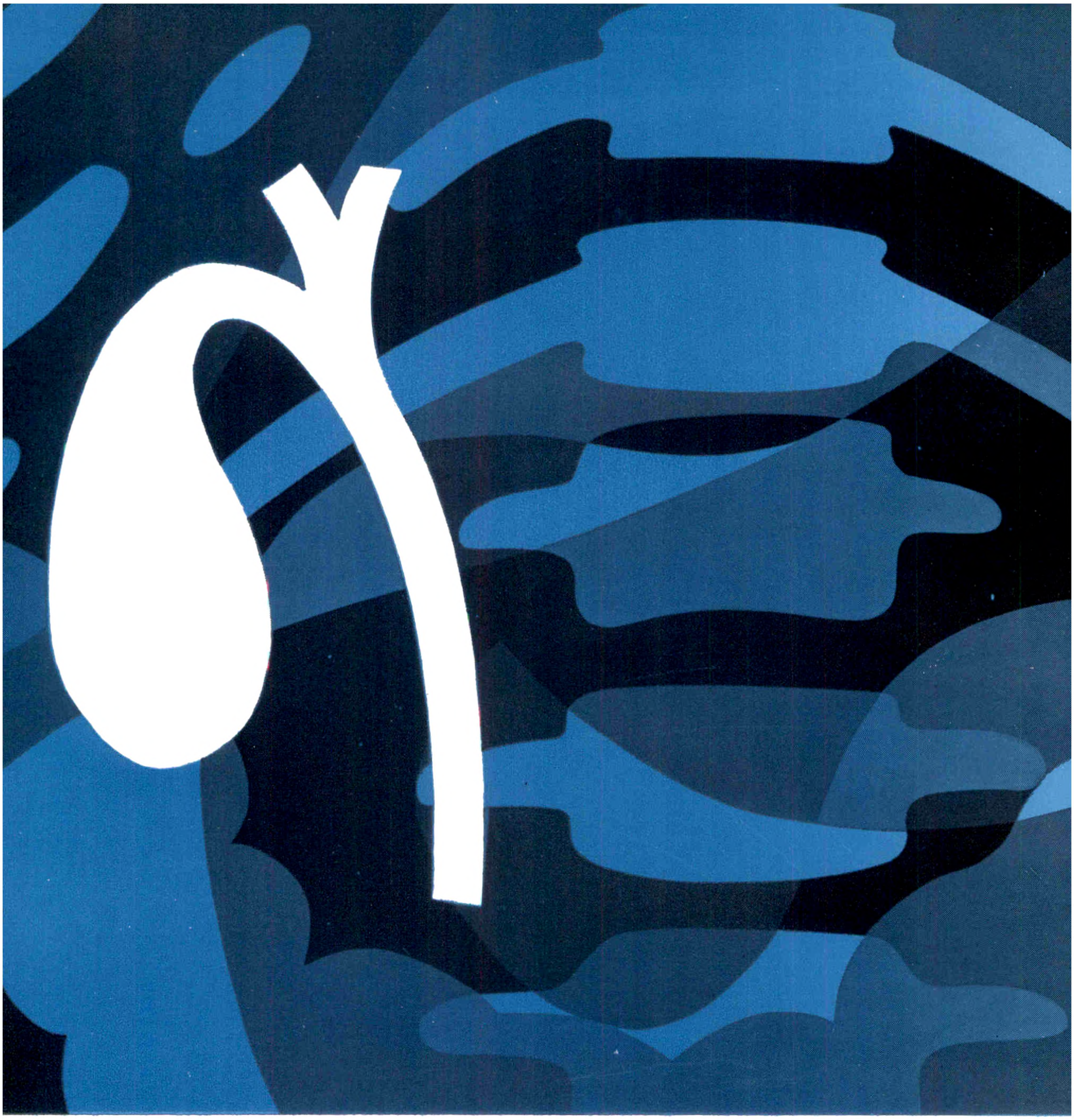

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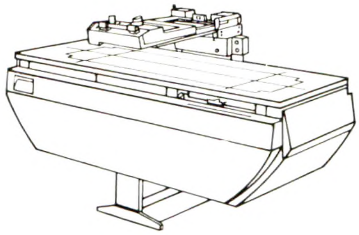

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*Time is
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New one-factor selection frees technician to concentrate on patient
kV

kV is the only factor your technician is required to select. Once that is done, she presses the exposure button and the automatic system does the rest.

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Only Norelco offers this system, which provides flawless radiographs automatically
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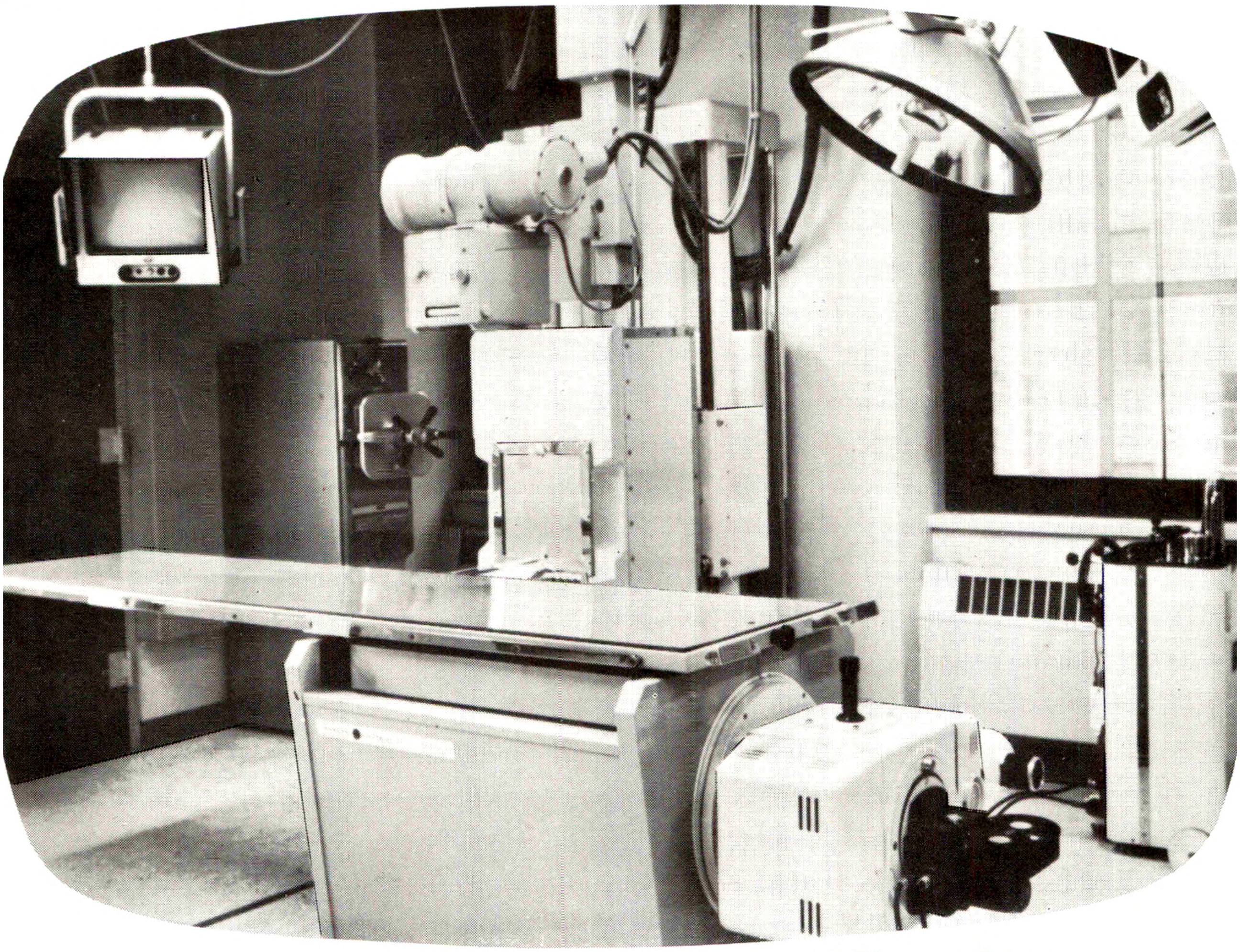

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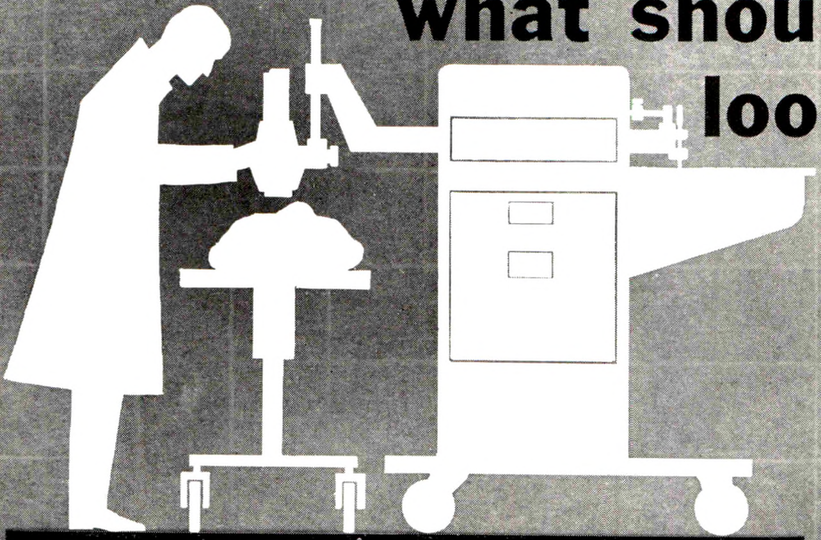
Odelca P-F Cameras and Accesso

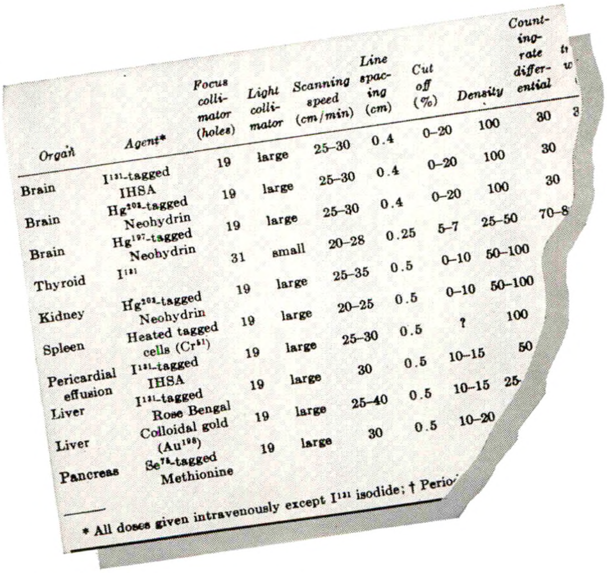
when investing in a scintillation scanner

what should you look for?



among other things...

wide-ranging *versatility*



Organ	Agent*	Focus collimator (holes)	Light collimator	Scanning speed (cm/min)	Line spacing (cm)	Cut off (%)	Density	Counting-rate differential	
Brain	I^{131}-tagged IHSA	19	large	25–30	0.4	0–20	100	30	3
Brain	Hg^{203}-tagged Neohydrin	19	large	25–30	0.4	0–20	100	30	
Brain	Hg^{197}-tagged Neohydrin	19	large	25–30	0.4	0–20	100	30	
Thyroid	I^{131}	31	small	20–28	0.25	5–7	25–50	70–8	
Kidney	Hg^{203}-tagged Neohydrin	19	large	25–35	0.5	0–10	50–100		
Spleen	Heated tagged cells (Cr^{51})	19	large	20–25	0.5	0–10	50–100		
Pericardial effusion	I^{131}-tagged IHSA	19	large	25–30	0.5	?	100		
Liver	I^{131}-tagged Rose Bengal	19	large	30	0.5	10–15	50		
Liver	Colloidal gold (Au^{198})	19	large	25–40	0.5	10–15	25		
Pancreas	Se^{75}-tagged Methionine	19	large	30	0.5	10–20			

---

* All doses given intravenously except I^{131} isodide; † Perio

the **simplicity** of a single chart guides technician in doing routine scans.

plus **versatility** for special scans of brain, thyroid, kidneys, liver, heart, spleen, lung, pancreas, parathyroid, and bone.

Of course you want your scanner to be easy to use, but not at the sacrifice of versatility. We think you should have full control over all parameters of the recording system, the pulse height analyzer, the scan travel speed, etc. so you can command wide-ranging capability for exploring new techniques or making special scans under difficult conditions.

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INTERNATIONAL REVIEW OF MEDICAL RADIOGRAPHY

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of recent developments in
field — have been most comp
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the contents of this new rad
logical review. Typical of
editorial makeup are articles
specialists of international
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Acta Genetica et Statistica Medica	14	13.50	q
Acta Haematologica (Int. Journal of Haematology)	31–32	13.50	m
Acta Psychotherapeutica et Psychosomatica (Int. Journal of Psychotherapy and Psychosomatics)	12	13.50	b
Angiologica (International Journal of Angiology) (New!)	1	13.50	b
Annales Paediatrici (Int. Review of Pediatrics)	202–203	13.50	m
Biologia Neonatorum (Neo-Natal Studies)	6–7	13.50	m
Cardiologia (Int. Archives of Cardiology)	44–45	13.50	m
Chemotherapia (International Journal of experimental and clinical Therapeutics)	8–9	13.50	m
Confinia Neurologica (Borderland of Neurology)	24	15.50	b
Confinia Psychiatrica (Borderland of Psychiatry)	7	9.25	q
Cytogenetics	3	22.80	b
Dermatologica (Int. Journal of Dermatology)	128–129	13.50	m
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Opthalmologica (Int. Journal of Ophthalmology)	147–148	13.50	m
Pathologia et Microbiologia (Swiss Journal of General Pathology and Bacteriology)	27	27.—	b
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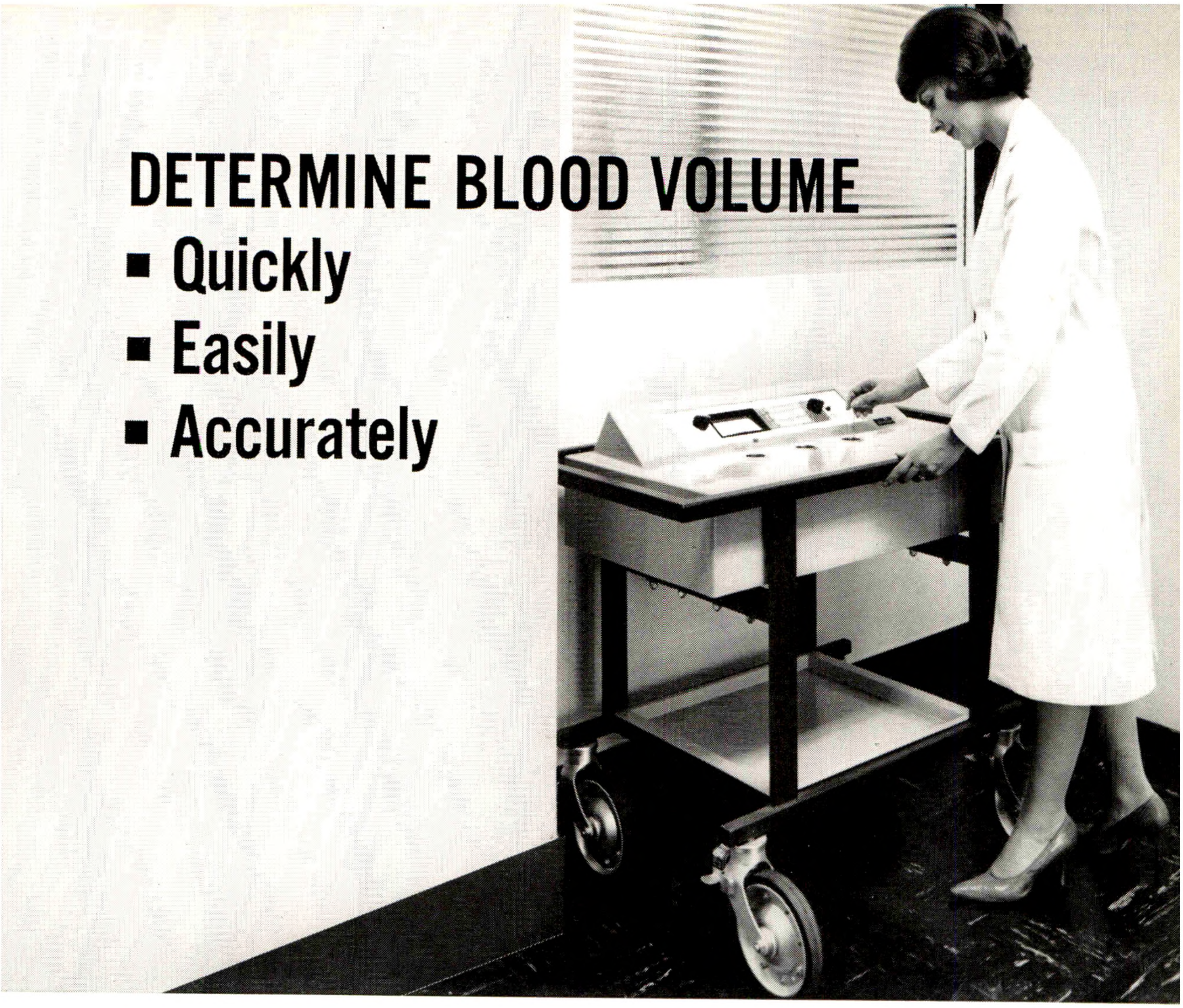

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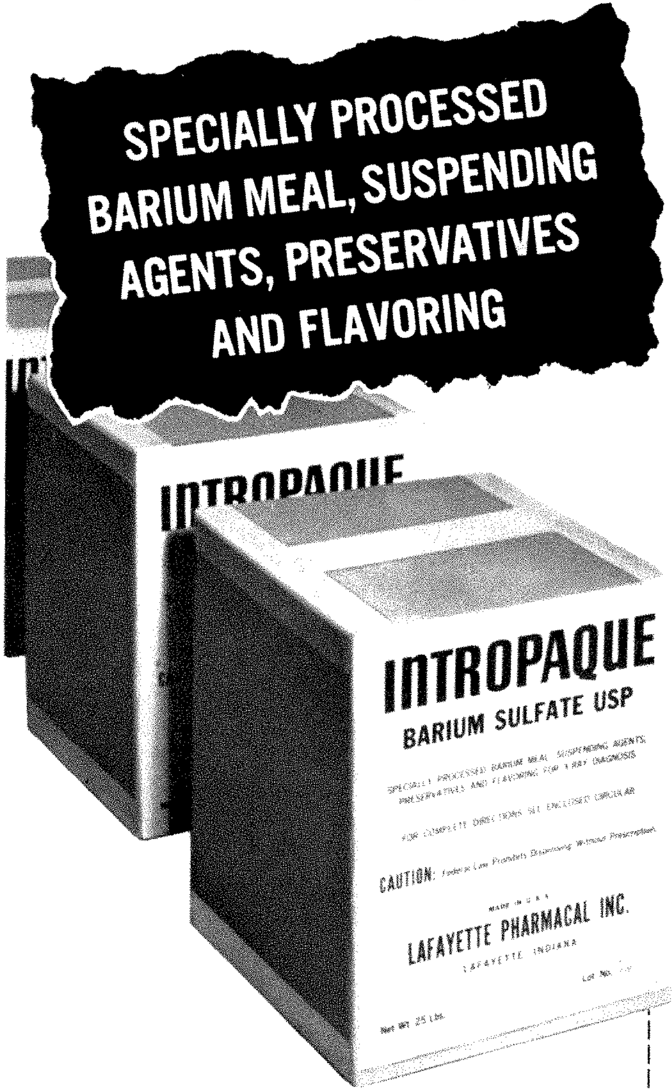

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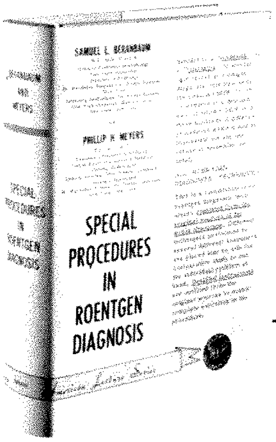

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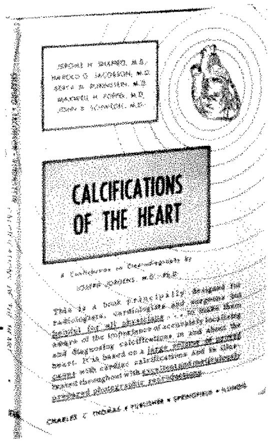

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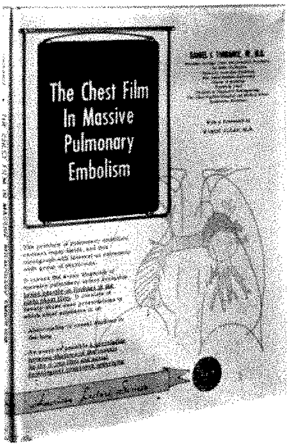

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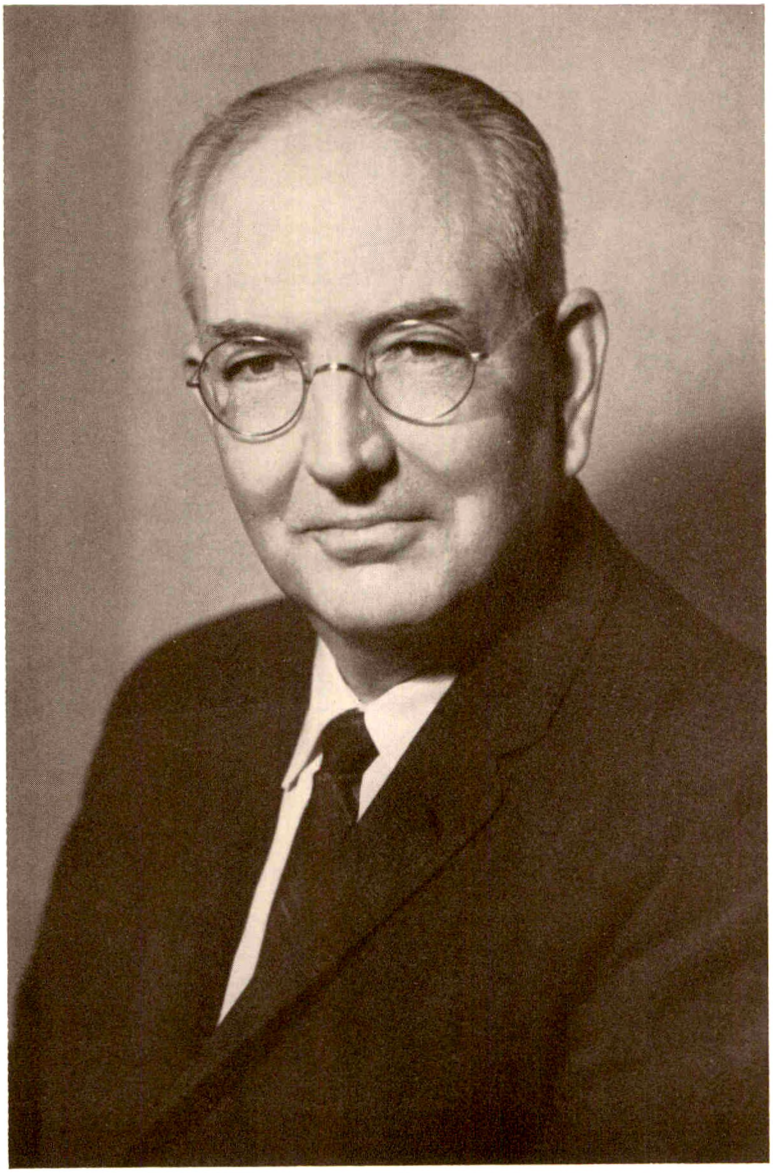

A. N. ARNESON

Janeway Lecturer, 1963

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LONG TERM FOLLOW-UP OBSERVATIONS IN CORPOREAL CANCER*

JANEWAY LECTURE, 1963

By A. N. ARNESON, M.D.
ST. LOUIS, MISSOURI

Dedication of an annual lecture to the memory of Henry Harrington Janeway is an honorable tradition of the American Radium Society that adds stature to the organization and prestige to the name it honors. I am grateful for the distinction to serve as your speaker upon this occasion, but it is unlikely that I shall muster a tribute equalling that which has been paid Janeway's memory by the more complete remarks of my predecessors. A thesis appropriate for discussion should consider Janeway's enthusiasm for radiation treatment as well as the stated aims of the Society. In looking back at the subject titles selected for earlier presentations, it is apparent that something peculiar has happened in San Francisco. The Society has twice met in this city since the lectureship was founded, and oddly enough both of those lectures dealt with the same subject. In 1938, Schmitz[17] *reviewed the history of treatment in cancer of the cervix, and in 1946 O'Brien*[16] *similarly discussed the radium treatment of that disease. This peculiarity of circumstance, perhaps overlooked by the Janeway Committee, gives me the fortuitous opportunity to sustain one of the lesser traditions of the Society by selecting a gynecologic subject for discussion this year.*

During Janeway's career the more surgically minded cited the treatment of endometrial cancer as a triumph for surgery in the management of malignant disease. Statistics were collected to show survival of 60 patients in every 100 submitted to hysterectomy. This did not take into account the substantial numbers of patients unsuited to surgery due to advance of disease or to poor physical status. Significant advance in radiation treatment came later when Heyman[9] *developed the so-called Stockholm method for "packing" radium tubes within the uterus. Clinical results began to rival those obtained by surgery. These events stimulated interest in improving the classification of patients into groups of more comparable clinical material for better assessment of therapeutic methods, and in the possibility for improving results among "operable" patients by combinations of radiation and surgery. In this country, due largely to members of this Society, interest was focused upon*

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* From the Department of Obstetrics and Gynecology and the Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri.

Presented at the Forty-fifth Annual Meeting of the American Radium Society, San Francisco, California, April 1-4, 1963.

the use of preoperative radium, but despite a relatively long trial the treatment of corporeal cancer remains in a more or less fluid state. Effectiveness of the combined treatment has never been fully ascertained. A degree of resolution may be achieved by utilizing methods of study currently in vogue. These include long term observation and the use of accumulative tables for statistical assessment.

ETIOLOGY OF CORPOREAL CANCER

THE natural response of normal endometrium to certain physiologic stimulations is a remarkable example of controlled growth. In addition to rapid repair and reconstruction following cyclical shedding, there is potential for hypertrophy during gestation. Benign endometrium may also undergo spread, either by invasion of uterine muscle or by dispersion to more distant points, with the displaced implants retaining their capability for physiologic response. Some benign forms of aberrant growth, notably the postmenopausal hyperplasias, are histologically similar to the more differentiated types of malignancy. This has long suggested the presence of intrinsic factors in the etiology of endometrial cancer. The close association of the disease with other disorders identified with pituitary responsibility adds support to this concept. There is a greater incidence of hypertension, obesity, diabetes and hirsutism than can be accounted for upon the basis of the advanced age of most patients. This has prompted speculation upon the probability that there is a particular type of female predestined to become a candidate for endometrial cancer.

Ovarian histology has yielded various findings that point toward a probable interrelationship between endometrial cancer and the endocrine organs. These include stromal hyperplasia and diffuse thecomatosis. A high incidence of cells resembling the interstitial cells of the testis has been noted by Sherman and Woolf[19] in the hilar regions of ovaries removed from patients with adenocarcinoma of the endometrium. They found Leydig cell hyperplasia in all cases specifically submitted to study and in 82 per cent of those reviewed after earlier operations, where representative segments of ovarian hilus had been included in the tissue sections. They also found a significant rise in luteinizing hormone. The authors postulate that a greater gonadotropic effect falls upon the abnormal Leydig cells as a result of menopausal loss of the follicular apparatus with its normal feed-back restraint upon the pituitary. This more sustained action is believed to stimulate the Leydig cells into hormonal production which, in turn, has an adverse effect upon endometrium. This causes the pituitary to excrete excessive amounts of gonadotropins. In the lack of feed-back control, there is stromal cell hyperplasia and concomitant carcinomatous change in the endometrium. The ovaries are believed to be identified with responsibility for the excessive excretion of luteinizing hormone. Surgical removal of these structures is followed by a drop in excretion not always present in patients treated by irradiation.

Among extrinsic factors believed important in etiology is the occasional example of corporeal cancer following irradiation for benign disease of the endometrium. If radiation acts carcinogenically upon endometrium, the incidence of subsequent malignant change should be broadly proportional to the amount of exposure. The incidence of corporeal cancer in such cases is not significantly different for the relatively high exposure to endometrium administered by intrauterine radium or the smaller amounts administered as external irradiation. Very large doses fall upon endometrium in the irradiation of cervical cancer. Two examples of corporeal cancer following treatment for cervical lesions are to be noted in the cases here reported, but in an earlier assessment dealing with cervical cancer there was only one example in approximately 400 patients followed for periods ranging from 5 to 20 years.[5,14] Previous exposure to radiation may be a causative factor in corporeal cancer, but it is equally probable that "precancerous" qualities are native to the endometrium in many cases of benign disease. Abnormal bleeding in such cases is controlled by an induced change in ovarian physiology. Hilar structures of the ovary are less susceptible to radiation injury than the more proliferative follicular system. In final analysis, it is probable that a disturbed endocrine system is responsible for the abnormal symptoms of benign disease as well as the subsequent occurrence of endometrial cancer.

Environmental factors, such as the associated effects of marriage and child bearing identified with cervical cancer, are less apparent in corporeal lesions. The results of examination in several thousand nuns have been reported by Towne.[20] The incidence of uterine cancer detected in those patients cannot be compared with the rate expected in the total population because age data are not included. It should be noted, however, that the incidence of corporeal cancer in one group is given as 6.6:1 that of the cervix, and in another as 11:1. Reversal of the usual ratio of those diseases in celebate women suggests a lesser association of endometrial cancer with some of the environmental factors identified with cervical lesions.

PROGNOSIS IN CORPOREAL CANCER

The strong evidence of intrinsic etiology in corporeal cancer prompts speculation upon some form of control by hormonal effects. This might act to lessen the risk of occurrence, or it might act to produce a reversal of growth with return of tumor to a more normal status. The obvious relationship to the endocrine organs has directed more than usual interest toward the weight of factors other than the stage of clinical advance on prognosis. The effect of morphologic histology on longevity has been an area of popular study. Mahle[12] published such a report in 1923, and Lindsay[11] made a similar study in 1927. Healy and Cutler[8] developed a classification of endometrial cancer on the basis of microscopic interpretation. Correlation of maturation with favorable end results in treatment was clearly shown for irradiation as well as for surgery. The relation of tumor differentiation to curability is more apparent in corporeal lesions than in many other human cancers. Size of the uterine body is also related to prognosis. Enlargement may be due to expansion by advanced growth of tumor, but it is more commonly caused by multiparity, subinvolution, or myoma. Healy and Brown[7] found that prognosis varies inversely with uterine size, and that the more adverse effects occur in patients treated by irradiation alone. Poor results are to be expected for any method of treatment in patients with disease advanced to a stage of uterine enlargement by tumor. Explanation of adverse effects is more difficult for other causes of enlargement. In the case of radiation treatment, the problem is largely one of dose distribution. An intrauterine tandem may necrotize adjacent tissue without affecting other areas of tumor made inaccessible by distortion or extension of the intrauterine space. Inadequacy of the tandem can be obviated by packing multiple sources within the cavity. Clinical results for that method are made almost independent of uterine size. Irregularity in the distribution of radiation does not apply to patients treated by surgery alone. The mechanics of enlargement may prompt dispersion in some cases, but it is more likely that stretching of the endometrial lining offers more linear space for spread. Prognosis declines with increase in volume of tumor.

A third factor significant in prognosis is tumor response to irradiation. This is not assessed on the basis of longevity alone, but can be detected in the better survival of patients showing a particular histologic response to preoperative irradiation. This has been demonstrated in previous publications reported in conjunction with Nolan and Sherman.[3,4,15,18] Preoperative "control," as measured by the microscopic disappearance of viable cancer in the removed uterus, occurred in approximately 70 per cent of the exposed patients. In that group the 5 year survival exceeded 80 per cent, but with evidence of "residual" cancer the rate was less than 50 per cent. The rate of radiation control was found to be somewhat greater in well differentiated lesions. Anaplastic tumors may have better capability for recovery from the effects of exposure, or by invasive qualities may penetrate the uterine wall for a distance shielding from radium. The dose usually necessary for control was first estimated to range between 5 and 10 threshold doses, but it was later assessed to be on the order of 7,000 r.

CLASSIFICATION OF CORPOREAL CANCER

Some authors contend that factors such as uterine size, tumor morphology, and radiation response are too unreliably separated from stage of clinical advance to give them independent status. It should be noted, however, that corporeal cancer does not lend itself to the more anatomic classification devised for cervical lesions. Postoperative classifications have been proposed, but these are not applicable to both radiologic and surgical treatment alike. Corporeal cancer is also associated with constitutional disorders that affect longevity as well as the method of treatment that can be applied. For these several reasons classification has usually included factors identified with prognosis. In collaborating with Sherman for an earlier report from our institution, we listed in order of significance 3 categories of prognosis: (1) small uterus—well differentiated tumor; (2) small uterus—anaplastic tumor, large uterus—well differentiated tumor; and (3) large uterus—anaplastic tumor.

The above classification is useful in prognosis, but it does not consider either stage of advance or physical condition. Those factors are included in the clinical staging proposed by Heyman and used in the International Classification of cancer of the uterus. It is in brief as follows: Stage I. The growth is confined to the uterus: (a) operation advisable; and (b) poor operative risk. Stage II. The growth has spread outside the uterus.

The International Classification keeps separately, for statistical purposes, those categories in which the cervix is involved by downgrowth of endometrial cancer (corporis et colli), as well as those in which it is impossible to state whether the tumor arose primarily in endometrium or in ovary. There is a final category for extensive pelvic disease due to an unidentified primary. Work is now in progress to revise the classification upon a more anatomic basis, and to specify more clearly the qualifications for Stage 0 as preinvasive adenocarcinoma. With revision, the cases formerly classed as corporis et colli may be included in general statistics, but until there is unanimity of opinion it would not seem advisable to deviate from the currently accepted classification.

CLINICAL RESULTS IN CORPOREAL CANCER

The clinical results for all cases of corporeal cancer have been reported for our institution in several earlier publications.[2,3,4,15,18] During the past 25 years, 1961 and earlier, a total of 173 patients have been examined with a view toward treatment under the private care of one individual. This group was selected for study in the belief that clinical evaluations in classification and in treatment have been more uniformly made. It should be noted, however, that the data to be presented are not necessarily indicative of the total results for the institutions at which the patients have been treated. At this point I should be remiss not to acknowledge the valuable assistance of Dr. Dan C. Mills in abstracting the case histories.

Six of the 173 patients have been deleted from study because treatment was omitted for reasons specified in Table I. The disease was too far advanced for treatment in 3, and 2 additional patients died of cardiac disease during treatment. One patient elected to go elsewhere so that she might receive treatment at a location nearer her home.

With tabulation of results made in the year 1962, there are 123 patients treated in 1957 and before who are subject to 5, 10

Table I

PATIENTS WITH CORPOREAL CANCER EXAMINED WITH A VIEW TOWARD TREATMENT

Clinical Stage	No. Examined	No. Treated	Refused Treatment	Went Elsewhere	Died before Treatment	Too Advanced
Ia	75	74	0	1	0	0
Ib	60	58	0	0	2*	0
II	14	12	0	0	0	2
C et C	24	23	0	0	0	1
	173	167	0	1	2	3

* Cardiac deaths.

and 15 year survival data given in Table II. The total number available for the 15 year report is small. For that time interval, the actual number of surviving patients is substituted for percentage values in each of the different clinical stages. It should be noted that none of the Stage II patients was found free of disease at even the 5 year period of observation. The fall-off in survival is less for Stage Ia than in any of the other groups, and the most rapid rate is found in Stage Ib. Those patients are supposedly in similar stages of advance. The discrepancy in survival must be assigned to differences in prognosis, differences in treatment, or to differences in longevity due to age and other associated factors. In that connection it is interesting to note that, despite a lesser survival rate at 5 years, the subsequent fall-off in corporis et colli cases progresses less rapidly than in Stage Ib cases.

There is weakness in the use of relative recovery rates for some areas of statistical assessment. The relative values represent only the percentage of cancer patients followed in a particular series who are found free of disease at a specified period of observation, and with longevity adequate for the time interval in question. End results measured by that method will vary in accordance with differences in treatment, in prognosis, in general physical condition of the patients, and in the completeness of the follow-up procedures. None of these factors can be individually tested by comparing the relative survival rates in different series of patients. An example of variables in age distribution, death by cancer or other intervening causes, and loss to follow-up can be seen in the scattergram shown in Figure 1. The data are for the 5 year values recorded in Table II. Three observations can be made. Patients alive and well at 5

Table II

RELATIVE CURE RATES FOR DIFFERENT STAGES

Clinical Stage	Five Years		Ten Years		Fifteen Years	
	No. Treated	Per Cent Survival	No. Treated	Per Cent Survival	No. Treated	Per Cent Survival
Ia	51	86.3	31	80.6	6	(4)*
Ib	44	59.1	23	35.0	6	(1)*
II	12	0	6	0	3	(0)*
C et C	16	31.2	9	22.2	2	(1)*
	123	61.0	69	50.7	17	35.3

* Substitution of patient numbers for percentages is shown ( ).

years' follow-up tend to fall in age groups of 55 years and younger. Death from intercurrent causes tends to occur in older patients. Lastly, the distribution of deaths due to cancer is more or less uniform throughout all age groups. If a line of separation is made between ages 55 to 60 years, a numerical count of living patients shows 42 in the younger group and 33 in the older. A count of deaths due to intercurrent causes, including the single case lost to follow-up, shows the division to be 2:12. The distribution ratio of death due to cancer is 16:18. The total group is rather evenly divided with 60 younger patients and 63 older.

The scattergram shows other data of interest. The clinically operable cases tend to fall into younger age groups. This is not an unexpected finding because factors responsible for a technically operable status are identified with more advanced age. All Stage I cases, both a and b, are relatively early lesions. The disease may have onset at any age, with the highest incidence falling in the postmenopausal period near age 55 to 60. There is, however, no evidence of age selectivity, in this series, for Stage II and corporis et colli patients. The recognition of advanced cancer at the time of clinical classification is evidence of delay in diagnosis. The various causes of delay are not identified with any particular age group. The lack of age specificity in the corporis et colli group, on the other hand, suggests the random distribution of a particular quality of tumor. It is apparent that these cases have a high rate of mortality. It may be presumed that cervical invasion is evidence of growth potential greater than that applying to other cases of endometrial cancer.

There is, finally, one additional point to be noted in reference to Stages Ia and Ib. There are 6 deaths due to cancer in the 51 patients classed as clinically operable. There are 7 such deaths in the 44 patients classed Stage Ib. These data represent the relative 5 year *failure* values in the two groups. The close agreement in numbers dead from cancer suggests equally effective treatment. This is not apparent in the accumulative survival data.

ACCUMULATIVE SURVIVAL DATA

The 5 year data shown by the scattergram in Figure 1 can be broken down into annual results for each successive year of follow-up by the use of accumulative survival tables. The procedure for constructing such tables is described in an earlier publication dealing with cervical cancer.[5] Special areas of interest, such as age distribution, can be investigated by developing separate data for each category. The results for each year of follow-up, or such other units of time as may be selected, are determined in accordance with the number of patients at risk. Patients at risk are those known to be alive and well for periods at least equal to the time period in question. The events recorded for each year show the number of patients alive and clinically free of cancer, those alive with or dead by cancer, those dead from intercurrent conditions, and the patients lost to follow-up observation. For the first year of post-treatment study, these various categories are taken as percentages of the total number at risk. Similar calculations are determined for each successive year in accordance with the decreasing numbers at risk, but the accumulative values are taken as percentages of the results in the immediate preceding year. As a consequence, the events in any particular year weigh upon the results for all subsequent time intervals. This method of study has the effect of considering all patients as if treated on the same date. That is not by itself important but it makes possible an increase in size of the sample, a means to detect any changing trend in clinical results due to the addition of recently treated patients, and an assessment of the rate of death due to the disease as well as to other intercurrent causes.

Accumulative survival tables have been prepared for 15 years' follow-up in all 167 patients treated in the year 1961 and before. The data are given in Table III. The accumulative per cent survival declines in

Table III

ACCUMULATIVE SURVIVAL DATA FOR ALL STAGES

Years at Risk	Patients Treated	Patients at Risk	Alive or Dead with Cancer		Dead of Intercurrent Disease		Lost to Follow-Up		Patients Alive and Well	Accumulative Survival Rate
			No.	Per Cent	No.	Per Cent	No.	Per Cent		
0–1	167	167	29	17.0	4	2.4	1	0.6	133	80.0
1–2	154	122	36	21.6	8	5.0	1	0.6	111	72.8
2–3	148	105	39	23.7	12	7.8	1	0.6	98	67.9
3–4	132	84	40	24.6	12	7.8	1	0.6	83	67.0
4–5	123	77	40	24.6	14	9.6	1	0.6	75	65.2
5–6	113	68	42	26.5	18	13.5	1	0.6	62	59.4
6–7	104	57	43	27.6	19	14.5	1	0.6	55	57.3
7–8	93	47	43	27.6	20	15.7	1	0.6	46	56.1
8–9	83	43	43	27.6	21	17.0	2	1.9	41	53.5
9–10	70	35	43	27.6	21	17.0	2	1.9	35	53.5
10–11	61	30	43	27.6	23	20.8	2	1.9	28	49.7
11–12	51	22	43	27.6	23	20.8	3	4.1	21	47.5
12–13	39	12	43	27.6	23	20.8	3	4.1	12	47.5
13–14	30	9	43	27.6	24	26.1	3	4.1	8	42.2
14–15	17	6	43	27.6	24	26.1	3	4.1	6	42.2
Plus	14									

accordance with the effect of successive events, but, due to decreasing numbers at risk, the proportional values representing an individual patient increase with extension of follow-up time. The accumulative tables show greater survival at 5, 10 and 15 years observation than the relative recovery rates. This is due to more favorable early results among the patients not yet observed for 5 years but added to the total sample.

Accumulative tables for the different clinical stages of corporeal cancer are shown in Tables IV, V and VI. The tables for Stage Ia and Ib show a significant difference in survival that is readily explained in the accumulative "deaths" for each group. The loss to follow-up is relatively unimportant. There is, however, a marked difference in deaths due to intercurrent conditions. In Stage Ib, the accumulative loss at 5 years observation is 21.6 per cent, with an increase to 39.2 per cent at 10 years. The respective values for Stage Ia are 1.5 per cent and 3.8 per cent, but it is interesting to note that a greater increase occurs in subsequent years. The younger patients common to the clinically operable group grow older with extension of the follow-up period. As they attain more advanced age, the attrition by intercurrent disease begins to increase. Stage Ib also shows a significantly higher death rate due to cancer. The accumulative value at 5 years is 17.7 per cent with a maximum of 22.8 per cent reached 2 years later. The maximum for Stage Ia is attained in the fourth year and is only 8.5 per cent. This difference is not apparent in the 5 year relative recovery rates taken from Figure 1. It is not entirely explained by the 2 cancer deaths and 1 patient currently alive with cancer among the 14 recently treated patients added to the accumulative table for Stage Ib. Of equal importance is the fact that cancer "death" has not occurred in any of the 23 patients added to Stage Ia. The accumulative data indicate that treatment is either less effective in Stage Ib, or that cases classed in that stage include cancers with a less favorable prognosis.

Accumulative tables for patients classed as Stage II, and as corporis et colli are shown

TABLE IV

ACCUMULATIVE SURVIVAL DATA FOR CORPOREAL CANCER CLASSED STAGE Ia

Years at Risk	Patients Treated	Patients at Risk	Alive or Dead with Cancer		Dead of Intercurrent Disease		Lost to Follow-Up		Patients Alive and Well	Accumulative Survival Rate
			No.	Per Cent	No.	Per Cent	No.	Per Cent		
0–1	74	74	4	5.4	0		0		70	94.6
1–2	68	64	4	5.4	0		0		64	94.6
2–3	65	61	5	7.0	1	1.5	0		59	91.5
3–4	55	49	6	8.5	1	1.5	0		48	90.0
4–5	51	44	6	8.5	1	1.5	0		44	90.0
5–6	45	39	6	8.5	2	3.8	0		38	87.7
6–7	42	35	6	8.5	2	3.8	0		35	87.7
7–8	37	31	6	8.5	2	3.8	0		31	87.7
8–9	34	29	6	8.5	2	3.8	1	3.0	28	84.7
9–10	31	25	6	8.5	2	3.8	1	3.0	25	84.7
10–11	26	22	6	8.5	3	7.5	1	3.0	21	81.0
11–12	22	17	6	8.5	3	7.5	2	7.4	16	76.6
12–13	14	10	6	8.5	3	7.5	2	7.4	10	76.6
13–14	10	7	6	8.5	4	18.1	2	7.4	6	66.0
14–15	6	4	6	8.5	4	18.1	2	7.4	4	66.0
Plus	5									

in Table VI. All of those in Stage II died from cancer within 2 years observation, or showed evidence of persistence from which they did not recover. Death due to cancer is also high in the corporis et colli group. The rate for the first year is 26.1 per cent, but due to the lesser effect of intercurrent disease the fall-off in accumulative survival after 5 years is less rapid than in Stage Ib. All of these factors were noted in the discussion of data shown in Figure 1.

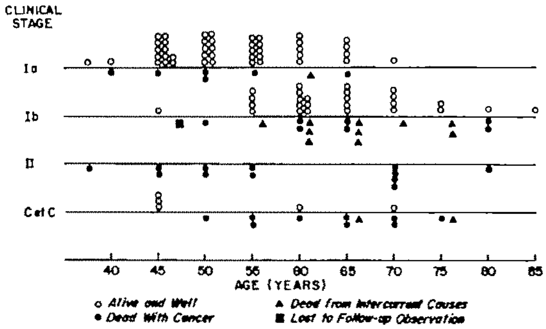

FIG. 1. Scattergram showing survival, and death due to cancer or to intercurrent causes, at 5 years' observation for the different clinical stages of corporeal cancer.

THE RATE OF CANCER DEATHS

The tabulated data can be transposed into graphic form to show in follow-up time the proportional effects of accumulative "deaths" on survival. A graph for all stages of corporeal cancer including the corporis et colli group is shown in Figure 2. The shaded area contracting with time is the accumulative survival rate. The other shaded areas expanding with time represent the losses in patients due to deaths by cancer, deaths from intercurrent causes, and attrition in numbers incurred by loss to follow-up observation. A similar graph has been published for the 4 clinical stages of cervical cancer.[5] This differs from corporeal cancer chiefly in the area of death from intercurrent causes which expands far less rapidly. It is interesting to note that the accumulative survival rates in the two series of patients are found to be almost identical. The curve for cervical disease is superimposed upon the graph shown in Figure 2. The deviation after the tenth year is due to an unfortunate loss to follow-up in

Table V

ACCUMULATIVE SURVIVAL DATA FOR CORPOREAL CANCER CLASSED STAGE Ib

Years at Risk	Patients Treated	Patients at Risk	Alive or Dead with Cancer		Dead of Intercurrent Disease		Lost to Follow-Up		Patients Alive and Well	Accumulative Survival Rate
			No.	Per Cent	No.	Per Cent	No.	Per Cent		
0–1	58	58	8	13.8	2	3.5	1	1.7	47	81.0
1–2	52	43	10	17.7	6	11.0	1	1.7	37	69.6
2–3	50	35	10	17.7	9	17.0	1	1.7	32	63.6
3–4	47	30	10	17.7	9	17.0	1	1.7	30	63.6
4–5	44	28	10	17.7	11	21.6	1	1.7	26	59.0
5–6	42	24	11	20.1	14	29.0	1	1.7	20	49.2
6–7	36	18	12	22.8	15	31.7	1	1.7	16	43.8
7–8	31	12	12	22.8	16	35.5	1	1.7	11	40.0
8–9	26	11	12	22.8	17	39.2	1	1.7	10	36.3
9–10	23	8	12	22.8	17	39.2	1	1.7	8	36.3
10–11	21	7	12	22.8	18	44.5	1	1.7	6	31.0
11–12	18	4	12	22.8	18	44.5	1	1.7	4	31.0
12–13	15	1	12	22.8	18	44.5	1	1.7	1	31.0
13–14	11	1	12	22.8	18	44.5	1	1.7	1	31.0
14–15	6	1	12	22.8	18	44.5	1	1.7	1	31.0
Plus	4									

the cervical cases after that period of observation. The shaded areas representing death by cancer expand rapidly in both diagrams. The maximal expansion is reached in the seventh year of observation in corporeal cancer, but not until the eleventh year in the case of cervical cancer. No examples of later recurrence are known to have developed in either the endometrial cases here reported nor in the cervical cases studied earlier. Furthermore, the greatest longevity with residual disease is found to be 8 years after primary treatment in corporeal cancer and 11 years in cervical lesions. It should be noted, however, that examples of later recurrence and of greater longevity with residual disease have been reported for both types of cancer. The apparent tendency for recurrence and cancer death to occur earlier in the fol-

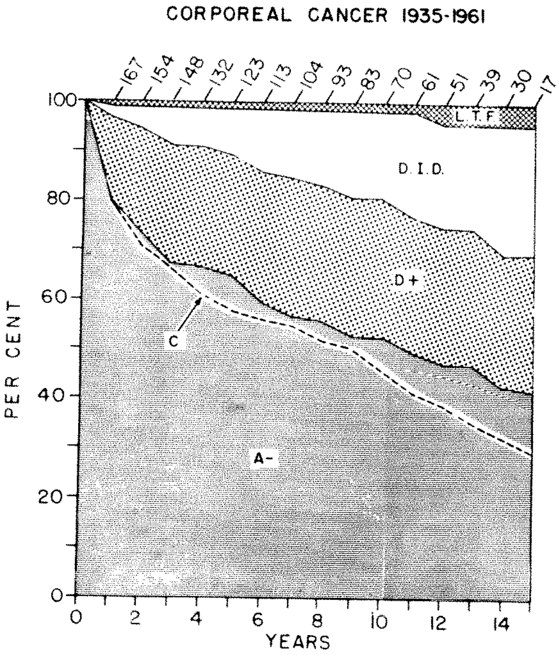

Fig. 2. Graphic presentation of accumulative survival data for all cases of corporeal cancer. A similarly determined survival curve for cervical cancer is shown upon the chart.

Table VI

ACCUMULATIVE SURVIVAL DATA FOR CORPOREAL CANCER CLASSED AS STAGE II, AND AS CORPORIS ET COLLI

Years at Risk	Patients Treated	Patients at Risk	Alive or Dead with Cancer		Dead of Intercurrent Disease		Lost to Follow-Up		Patients Alive and Well	Accumulative Survival Rate
			No.	Per Cent	No.	Per Cent	No.	Per Cent		
Stage II										
0–1	12	12	11	90.0	0		0		1	9.1
1–2	12	1	12	100.0	0		0		0	0
2–3	12	0	0		0		0		0	0
Corporis et Colli										
0–1	23	23	6	26.1	2	8.7	0		15	65.2
1–2	22	14	10	44.7	2	8.7	0		10	46.6
2–3	21	9	12	55.1	2	8.7	0		7	36.2
3–4	18	5	12	55.1	2	8.7	0		5	36.2
4–5	16	5	12	55.1	2	8.7	0		5	36.2
5–6	15	5	13	62.3	2	8.7	0		4	29.0
6–7	15	4	13	62.3	2	8.7	0		4	29.0
7–8	14	4	13	62.3	2	8.7	0		4	29.0
8–9	12	3	13	62.3	2	8.7	0		3	29.0
9–10	9	2	13	62.3	2	8.7	0		2	29.0
10–11	8	1	13	62.3	2	8.7	0		1	29.0
11–12	6	1	13	62.3	2	8.7	0		1	29.0
12–13	5	1	13	62.3	2	8.7	0		1	29.0
13–14	4	1	13	62.3	2	8.7	0		1	29.0
14–15	2	1	13	62.3	2	8.7	0		1	29.0
Plus	2									

low-up of endometrial lesions may explain an observation noted in the Annual Report on the Results of Treatment in Carcinoma of the Uterus for data collated in 1961.[10] In testing the stability of recovery after 5 years' observation, the Editors found a lesser risk of recurrence in carcinoma of the corpus. This is also apparent after correction for deaths due to intercurrent disease. There is, of course, a much higher rate of death from that cause in endometrial cases, but the Editors find, "the corrected survival rates prove to be almost perfectly exponential, their logarithms being straight lines." A greater survival rate is reported for corporeal cancer but the rates appear essentially equal if, as has been done in the accumulative data reported here, there is no correction for intercurrent deaths and corporis et colli patients are included.

The *rate* of cancer deaths is important in any statistical attempt aimed at testing the effectiveness of treatment. This is particularly important for disease in patients showing a high rate of attrition from other causes. Relative recovery rates have weakness in this area. In developing the accumulative tables for this report, patients have been removed from the "alive and well" category upon the detection of recurrence, but transference to the "alive or dead with cancer" category may not coincide with the actual year of death. Both time intervals are important. Since data in the accumulative tables really represent the rate of detection of recurrence, the values for early observations are higher than the actual rate of death. When plotted on curves as shown in Figure 3, the points are found irregularly distributed along sharply rising lines that become parallel after the seventh year. The percentage of treatment failure is greatest in Stage II. The failures in Stages Ia and Ib are fewer than in the corporis et colli group, but the incidence for technically operable patients is more than double that for those in whom hysterectomy can be performed. A difference can also be noted in each stage for the time interval after treatment necessary for detection of the full recurrence rate. In Stage II the interval is between 1 and 2 years. In Stage Ia it is 2 to 3 years. The interval for the corporis et colli group is 3 to 4 years, but in Stage Ib it is 6 to 7 years.

Patients currently alive with active disease present a problem in plotting curves to show the actual rate of death by cancer. All of the Stage II cases were dead at the time of final assessment in 1962, but 2 patients in other stages were alive with persistent cancer. One, classed corporis et colli, was treated in 1959. The other patient, treated in 1961, is in Stage Ib. For convenience, these are counted as dead at 3 and 1 years after treatment and included with the actual number of patients dying in successive years of follow-up as shown in Table VII. Due to the small number of patients in each category, there are follow-up years in which cancer death did not occur, but it is apparent that a graph showing the percentage rate of death would follow a sigmoid curve. This is shown in Figure 4, but, due to overlapping points for Stages Ia, Ib and corporis et colli, a single composite curve is drawn for those clinical groups. The various points are in good agreement for the first 2 years of follow-up, but there is considerable divergence after that time interval. Fifty per cent of all cancer deaths occur within a period slightly

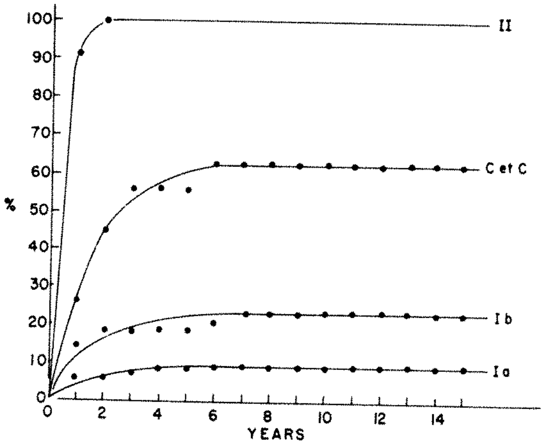

Fig. 3. Accumulative rates of death due to cancer in the different clinical stages.

Table VII

NUMBER OF DEATHS DUE TO CANCER ACCORDING TO CLINICAL STAGE

Years at Risk	Clinical Stage			
	Ia	Ib	II	C et C
0–1	1	2	6	2
1–2	2	3	3	4
2–3	0	2	2	3
3–4	1	2	1	1
4–5	0	0	0	2
5–6	2	0	0	1
6–7	0	2	0	0
7–8	0	1	0	0
Total	6	12	12	13

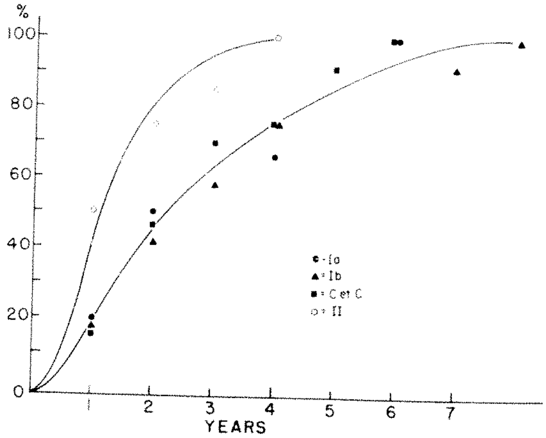

Fig. 4. Accumulative per cent death due to cancer at different periods of observation in the different clinical stages. A single composite curve is shown for Stages Ia, Ib, and corporis et colli cases.

greater than 2 years' observation. In Stage II that increment is attained at 1 year. Despite this difference in rate of death, the curves are believed to be only a function of stage of clinical advance. Data on this small number of cases do not show a significant difference in the rates of dying as indicated by the slopes of probit lines. In other words the rates of dying after treatment may be essentially the same. It is more likely that differences in specific mortalities can be attributed to the temporal relationship of treatment to onset of the disease. These data confirm that the division of corporeal cancer into 2 stages of clinical advance is broadly made by the International Classification. The corporis et colli group appears to correlate more closely with Stage I, but it is surprising that the high incidence of treatment failure among these patients fails to show a more rapid rate of cancer death. This is an observation that should be studied for confirmation in a larger series of patients. Specific conclusions cannot be developed here, but a random distribution of unrecognized causes of treatment failure may be responsible for the relatively uniform rates of cancer death. In reviewing the clinical records for deceased patients in this series, corporeal cancer is found to cause death chiefly by intra-abdominal disease. Patients classed Stage Ia and corporis et colli show a tendency toward a somewhat greater incidence of distant dispersion. This might be expected in clinically operable patients. Elimination of pelvic disease by hysterectomy results in treatment failure only when spread has preceded surgery. Greater capability for dispersion may be native to endometrial tumors invading the cervix. Patients who proved treatment failures in these 2 stages died somewhat more promptly than those who were failures in Stage Ib. It is also possible that tumor morphology, size of the uterus, and histologic response to irradiation may not only affect curability, but may also be factors tending to obliterate differences in the rate of dying by their random distribution in the different clinical stages.

END RESULTS ACCORDING TO TUMOR MORPHOLOGY

Adenocarcinomas of endometrium can, with the exception of adenoacanthomas, be divided into 4 different grades of histologic differentiation.[8] The highest forms of differentiation are represented in the adult characteristics of the adenoma malignum, Type I and II. Moderate undifferentiation is found in the adenocarcinoma, Type III. The more undifferentiated, Type IV, lesions are anaplastic. Pure forms are rare. In the mixtures that occur, there is usually one type that tends to predominate. In Table VIII the prevailing form has been used to classify patients into 3 stages of histologic differentiation. Survival figures are taken from accumulative data tables for Stages

TABLE VIII

NUMBER OF DEATHS DUE TO CANCER ACCORDING TO CLINICAL STAGE AND HISTOLOGY

Histology	Clinical Stage					
	Ia		Ib		C et C	
	Treated	Dead	Treated	Dead	Treated	Dead
Adenoacanthoma	3	0	0	0	1	1
Well Differentiated	48	1	33	1	10	4
Moderate Undifferentiation	17	2	18	6	8	5
Anaplastic	6	3	7	5	4	3
Total	74	6	58	12	23	13

1a and 1b, and for the corporis et colli group.

There are 91 lesions interpreted as showing a high degree of differentiation. Only 6 deaths are recorded in that group. One occurred among the 48 patients staged 1a, 1 among the 33 staged 1b, and 4 among the 10 classed in the corporis et colli group. A higher incidence of treatment failure is found among the undifferentiated lesions. There are 13 deaths recorded for the 43 patients showing moderately undifferentiated lesions, and 11 deaths recorded for the 17 patients showing anaplastic lesions. These data are in accordance with those given in earlier reports. The well differentiated lesion responds with favorable curability for treatment by surgery alone, by irradiation alone, or by a combination of both methods. It is, however, of interest to note the differences in incidence of treatment failure for undifferentiated lesions in the various clinical stages. In Stage 1a there are only 5 deaths among the 23 patients showing various degrees of undifferentiation. In Stage 1b there are 11 deaths for the 25 patients showing similar types of lesions. The fact that hysterectomy was employed with or without preoperative irradiation in practically all of the Stage 1a patients suggests that the addition of surgery may be important in the management of undifferentiated forms. This can only be assumed, however, because proof of an otherwise comparable material is lacking.

There are, in summary, two points in reference to the data given in Table VIII. It should first be noted that 80 per cent of all cancer deaths are found among the patients presenting poorly differentiated lesions. Of equal importance is the fact that the incidence of treatment failure is proportional to the distribution of those histologic types. Evidence of poor differentiation is found in 31 per cent of the patients classed Stage 1a, in 43 per cent of those staged 1b, and in 52 per cent of the corporis et colli group. It is apparent that treatment failure is related to tumor morphology, but longevity with persistent cancer is related to stage of tumor advance.

The adverse effects of uterine size upon prognosis have been studied in conjunction with the effect of tumor morphology. This is not believed significant in this series of cases for two reasons. In the first place, the incidence of uterine enlargement is about equally distributed among all categories of classification. The over-all incidence is approximately 10 per cent. In the second place, the effect of uterine size upon prognosis is believed nullified by use of the "packing" technique of radium treatment. That method, with or without surgery, was employed for all patients showing any clinical degree of enlargement.

END RESULTS ACCORDING TO RADIATION RESPONSE

The radiation response of tumors can be histologically determined by examining uteri removed after the application of preoperative radium. Degenerative changes resulting in total disruption of all cellular elements of the tumor present reasonable evidence of radiation "control" of the local area. Identifiable cancer cells, or the detection of severely injured cancer cells, have been taken as evidence of "residual" disease. Hysterectomy has been employed only in Stage 1a patients, but 19 of the 74 in that stage have been treated by surgery alone, and in 4 hysterectomy was not performed after the initial application of radiation. Among the 51 patients submitted to the "combined" procedure, there were 38 examples of "control" and 13 examples of "residual" disease. These data are given in Table IX with separation of the 51 lesions into different grades of differentiation. In this table all of the 74 patients in Stage 1a can be accounted for under treatment by the combined procedure or by surgery alone except 4 in the well differentiated group managed by irradiation alone. Failure to gain "control" by preoperative radium is significantly higher among the undifferentiated types of tumor.

The effect of radiation "control" on curability is tested in Table X by the use of 5 year recovery rates. Through 1957, and

TABLE IX

INCIDENCE OF RESIDUAL CANCER ACCORDING TO HISTOLOGY IN STAGE Ia CASES RECEIVING COMBINED TREATMENT

Histology	No. of Patients	"Residual" Cancer	Hysterectomy Only
Adenoacanthoma	1	0	2
Well Differentiated	32	4	12
Moderate Undifferentiation	14	7	3
Anaplastic	4	2	2
Total	51	13	19

earlier years, there were in Stage I a total of 34 patients submitted to the combined procedure, 13 treated by surgery alone, and 4 managed by irradiation alone. Surgery was omitted in the latter group of 4 patients for specific reasons. One refused operation, and in another hysterectomy was omitted due to thrombophlebitis that followed radium treatment. In the 2 remaining patients, surgery was first delayed due to untoward radiation reactions, and then finally omitted. All of these 4 patients presented well differentiated lesions. In 3 there was significant enlargement of the uterus. These are alive and well for periods of 13, 16, and 20 years following treatment. The single cancer death occurred in a patient with a uterus of normal size. There is, therefore, a 5 year survival of 3 out of 4 patients. Among the 13 patients treated by hysterectomy alone, there is a 5 year survival of 11, or 84.6 per cent. The 34 patients submitted to the combined treatment show a difference in survival in accordance with "control" or "residual" tumor effects following preoperative radium. Only 2 deaths have occurred at the 5 year period of observation among the 26 patients with "control." One patient died from intercurrent causes, and the other presented a moderately undifferentiated lesion. Of the 8 with "residual" tumor, there are 6 survivors at 5 years' observation. Both of the patients dying from cancer presented anaplastic lesions.

TABLE X

RELATIVE FIVE YEAR SURVIVAL ACCORDING TO METHOD OF TREATMENT IN CLINICAL STAGE Ia

Treatment	No. of Patients	Alive and Well	Per Cent
Combined			
"Control"	26	24	92.3
"Residual"	8	6	75.0
	34	30	88.2
Surgery Alone	13	11	84.6
Irradiation Alone	4	3	75.0
	51	44	86.3

These data do not show a significant difference in survival for different methods of treatment. Neither have the earlier reports from our institution shown a valid difference in the end results for surgery alone versus the combined procedure. The well differentiated lesions have always shown the highest survival rate, with the patients alive and well at 5 years' observation, including 10 per cent to 15 per cent of those with "residual" tumor. Patients with lesions of poor differentiation have shown survival rates of approximately 50 per cent, with almost half of those presenting evidence of "residual" cancer in the removed specimens. The key to the importance of the combined procedure is found in earlier experience. Anaplastic lesions treated by surgery alone show a recovery rate of about 1 in every 3 patients. Following the combined procedure the rate is approximately 2 of every 3 patients, with an incidence of "control" on the order of 50 per cent. The 5 year survival among all patients with "control" has averaged about 90 per cent for all

TABLE XI

ACCUMULATIVE SURVIVAL DATA FOR STAGE Ia TREATED BY SURGERY OR COMBINATION OF RADIUM AND HYSTERECTOMY

Years at Risk	Patients Treated	Patients at Risk	Alive or Dead with Cancer	Dead of Intercurrent Disease	Lost to Follow-Up	Patients Alive and Well	Accumulative Survival Rate
			Surgery Alone				
0–1	19	19	2	0	0	17	89.4
1–2	18	16	2	0	0	16	89.4
2–3	17	15	2	0	0	15	89.4
3–4	14	12	2	0	0	12	89.4
4–5	13	11	2	0	0	11	89.4
5–6	10	9	2	0	0	9	89.4
6–7	8	7	2	0	0	7	89.4
7–8	8	7	2	0	0	7	89.4
8–9	7	6	2	0	0	6	89.4
9–10	6	5	2	0	0	5	89.4
Plus	6						
			Combined Treatment				
0–1	51	51	2	0	0	49	96.0
1–2	46	44	2	0	0	44	96.0
2–3	44	42	2	1	0	41	93.6
3–4	37	34	3	1	0	33	90.6
4–5	34	30	3	1	0	30	90.6
5–6	31	27	3	2	0	26	87.6
6–7	30	25	3	2	0	25	87.6
7–8	25	21	3	2	0	21	87.6
8–9	23	20	3	2	1	19	83.2
9–10	21	17	3	2	1	17	83.2
Plus	16						

histologic types. It is, therefore, apparent that cure rates are improved with "control" of tumor by preoperative irradiation. An irradiation technique that will increase the incidence of "control" will advance the recovery of patients. A greater tumor effect is expected for preoperative radium than for external irradiation, but lethal tumor doses cannot be attained in all patients without increase in the incidence of sequelae due to the combined trauma of both irradiation and surgery.

END RESULTS ACCORDING TO TREATMENT

ACCUMULATIVE DATA

The 5 year data given in Table x show a survival rate of 88 per cent for the combined treatment and approximately 85 per cent for management by surgery alone. For the numbers of patients in question, this is not a difference of statistical significance. An attempt is made in Table xi to utilize accumulative data in comparing the two methods of treatment. This method also fails to show a significant difference in results. When tested for confidence levels, the probability for the results shown is on the order of 5 out of 10 chances.

There are, however, certain differences in prognosis that should be noted for the two methods of treatment. One of these applies to size of the uterus. All of the patients treated by surgery alone presented uteri of normal size. There are 7 examples of uterine enlargement among the 51 submitted to the combined procedure. A second difference

Table XII

MAJOR COMPLICATIONS FOLLOWING TREATMENT OR DUE TO CANCER ACCORDING TO CLINICAL STAGE

Clinical Stage	Complication	Treatment
Ia	Intestinal obstruction	Resection of bowel
Ia	Rectal reaction	Colostomy Exenteration
Ib	Rectal reaction	Colostomy
Ib	Intestinal obstruction due to tumor	Resection of bowel
C et C	Rectal reaction	Colostomy
C et C	Abscess—rectal reaction	Colostomy

applies to patient attrition by intercurrent disease or by loss to follow-up. There are no losses from those causes among the patients treated by surgery alone, but in the combined treatment group there are 2 deaths from intercurrent disease and one patient lost to follow-up after the eighth year. If those 3 patients are deleted from the data, the accumulative survival result for the combined treatment becomes 93 per cent after the third year. Finally, it should also be noted that the effect of poor tumor differentiation weighs slightly heavier upon the combined treatment group. These data emphasize the difficulty in establishing uniformity in clinical material. The patients submitted to management by surgery alone were carefully selected. The choice was not wisely made in the 2 examples of death from cancer. One of those patients presented endometrial cancer that developed after earlier irradiation for cervical cancer. The other patient had been irradiated for benign disease. Cancer had spread outside the uterus in both instances, but the preoperative classification as Stage Ia was not altered. It is apparent that surgery alone is adequate treatment for patients presenting early lesions of a well differentiated type in uteri of normal size. It is equally apparent, however, that the adverse prognostic effects of uterine enlargement and tumor undifferentiation necessitate the use of preoperative irradiation.

COMPLICATIONS

The incidence and severity of complications is important in determining clinical results. Injury may be due to treatment but it can also be a consequence of the disease itself. There is little difference to be noted in complications for corporeal and cervical cancer except in the incidence of fistula formation. The risk of bladder and rectal injury is increased in cervical cancer by the necessity for larger amounts of radium radiation applied within the vagina. The close proximity of those structures to the cervix also increases the risk of tumor invasion. The other structures apt to be injured, chiefly bowel, are essentially the same in both types of cancer.

Combinations of irradiation and surgery are known to increase the risk of complication.[1,13] Chau, Fletcher, Rutledge and Dodd[6] have attempted to assess dose levels of radiation exposure compatible with different degrees of surgical management. Patients submitted to the combined procedure here reported have not experienced an unfavorable complication rate because dose levels have been less than those applied to patients managed by irradiation alone, and by the fact that the surgical procedure has usually been less extensive than radical hysterectomy with lymph node dissection. There have been only 2 examples of severe complication among the 51 patients, as shown in Table XII. The subsequent management of one included small bowel resection due to obstruction considered to be a complication of treatment. The other patient is a single example of death due to complications following treatment that were largely the effect of irradiation. Prior to the diagnosis of cancer, this patient had been treated surgically for endometriosis. Considerable fibrosis persisted after management of corporeal cancer by the combined procedure. Additional external irradiation was applied by betatron. A large bowel fistula was controlled by colostomy which was followed later by pelvic exenteration. Death occurred several weeks later.

Two major complications occurred among the 58 patients classed Stage Ib and managed by irradiation alone. Colostomy was performed for a severe rectal reaction in one, and bowel resection was performed for intestinal obstruction due to metastatic tumor in the other.

The rate of severe complication was greatest among the 23 patients classed corporis et colli. A severe rectal reaction necessitated colostomy in one. The other patient developed a severe rectal reaction due to diverticulosis with formation of pelvic abscess that involved the abdominal wall.

DOUBLE PRIMARY CANCERS

Among 374 primary cancers of the cervix followed for periods of 5 to 20 years, we found a total of 11 patients with second primary lesions. In one additional instance there was a separate primary of the breast that preceded treatment for cervical cancer.[5] Among the 167 corporeal cancers followed for 1 to more than 15 years, there were 4 patients with primary cancer in other structures diagnosed before treatment for corporeal cancer. In 2 patients a second primary had been diagnosed after treatment of the corporeal lesion. These data are given in Table XIII. In 2 patients additional lesions were concurrent with the diagnosis of endometrial cancer.

Table XIII

OTHER PRIMARY TUMORS NOTED AMONG PATIENTS WITH CORPOREAL CANCER

Concurrent	First Primary	Second Primary	Interval (Years)
	Mammary	Corporeal	2
	Mammary	Corporeal	0.5
	Cervical	Corporeal	8
	Cervical	Corporeal	4
	Corporeal	Bladder	1
	Corporeal	Colon	12
Cervical (*in situ*)			0
Ovary (serous cystadenoma)			0

SUMMARY AND CONCLUSIONS

1. The over-all curability of corporeal cancer is essentially equal to that of cervical cancer, but the patients die from different causes. The proportion of deaths due to cancer is greater in the case of cervical lesions, but the proportion of deaths due to intercurrent causes is greater in the case of corporeal cancer.

From the patient data here reported, there is evidence that recurrence of corporeal cancer tends to occur at earlier time intervals in follow-up than was noted in a similar study of cervical cancer. As a result of that difference, a patient with corporeal cancer found to be free of recurrence at 5 years' observation appears to have less risk of later reappearance of the same cancer than does a similar patient with cervical cancer observed for an equal period after treatment.

2. The curability of corporeal cancer varies inversely with stage of clinical advance, as is true for all other types of malignant disease. There are, however, specific factors that affect the control of corporeal cancer in the different categories of clinical classification. These are, in the order of their importance: tumor morphology, response to radiation, and size of the uterus. Radiation response is largely a function of tumor morphology. The significance of uterine enlargement in prognosis is essentially eliminated by special radium techniques that use the "packing" method. It is thus apparent that the degree of tumor differentiation is second in importance only to stage of clinical advance in determining the results of treatment. The incidence of failure is largely the result of variations in the distribution of lesions with poor differentiation. Among the patients here reported, those classed Stage Ia (clinically operable) showed 31 per cent with poor differentiation. Among those classed Stage

Ib (technically operable), the rate is found to be 43 per cent, and in the corporis et colli group it is 52 per cent. None of the Stage II patients was considered free of disease after treatment; all but 1 died within the first year of observation. Longevity with persistence of cancer after treatment is, in all clinical classes, a function of stage of tumor advance.

3. The behavior of corporeal cancer with downgrowth into the cervix presents clinical differences that qualify such cases for classification into a particular category, but their natural history does not warrant segregation into a group kept statistically separate from other cases. The classification developed by the Cancer Committee of the International Federation of Gynecology and Obstetrics should be supported. This, in brief, considers as Stage I those patients in whom the tumor is confined to the corpus. In Stage II the cancer involves the corpus and cervix. Qualification for Stage III necessitates spread outside the uterus but not outside the true pelvis. In Stage IV there is extension outside the true pelvis, or obvious involvement of the mucosa of the bladder or rectum. This classification for corporeal cancer is in line with that employed for cervical cancer and deletes the addition of factors related to physical condition such as "clinically" or "technically" operable.

4. Patients with corporeal cancer suited to surgical management can be successfully treated by hysterectomy if the uterus is of normal size and if the tumor presents histologic evidence of high differentiation. Preoperative radium treatment contributes an improvement in results when the above specified conditions are not present. External irradiation can be added, when indicated, as a postoperative measure, but must be employed in conjunction with radium treatment in all patients not to be managed surgically. Complications of the combined procedure increase with the amount of radiation applied as well as with increase in the radical extent of surgery. The complication rate for corporeal cancer is not significantly different from that for cervical cancer except that for endometrial lesions there appears to be less risk of bladder and rectal fistula.

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RADIATION FOR THERAPY—IN RETROSPECT AND PROSPECT*

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CAMBRIDGE, MASSACHUSETTS

MANY members of this Society have contributed to the medical radiation background on which these reflections are based. One of the foremost was Dr. George Winslow Holmes whom we remember and honor on this annual occasion. It is with a deep sense of privilege and pleasure that I recall this kindly physician who influenced so richly the spirit and practice of radiology in this country.

Dr. George Holmes was already a senior radiologist and distinguished teacher when I first heard him speak at the Massachusetts Institute of Technology (MIT) in 1934 on the effects and dangers of radiation. Not long thereafter a more private meeting took place at the Massachusetts General Hospital with Dr. Holmes surrounded by a small circle of staff and residents in radiology. Three of us from MIT, physicists Robert J. Van de Graaff and Edward S. Lamar, and I—a research associate in electrical engineering—had come to learn about the use of x rays for therapy and to suggest the feasibility of producing very high voltage x rays with Van de Graaff's new belt type of electrostatic generator.

This was the beginning of my orientation in radiation therapy. Months later, one sunny afternoon in the spring of 1935 a radiologist called at my laboratory. He had heard of our assertions regarding the Van de Graaff belt generator and wondered if it could power a 400 kv. therapy tube. My parting remark to Dr. Richard Dresser now seems rather brash. "Make it a million volts" I said as he left, "and we *might* be interested." In those days one million volts for x ray production loomed like the summit of Mt. Everest—fascinating and unscaled. With Van de Graaff's refreshingly sound and direct ideas on electrostatic generation, we were confident that it could be attained. And behind the challenge of million volt operation was the promise of greatly improved radiation quality and intense x ray output.

Dr. Dresser, then chief radiologist at the Huntington Memorial Hospital, came back the next afternoon and made it a million. But warned by others that electrostatics was all volts and no amperes, he now wanted evidence that sufficient x ray output would be available.

NUCLEAR SCIENCE IN THE 1930S

Back in the 1930s, nuclear physics was still very new. By studying the scattering of alpha particles passing through thin gold films, Rutherford had deduced the first clear picture of the atom. A miniature solar system, its exceedingly tiny nucleus contained virtually all of the atomic mass and all of the positive charge. At relatively great distance this nuclear kernel was encircled by an appropriate swarm of negative electrons. Applying Planck's quantum theory to this picture, the Danish theoretician, Niels Bohr, formulated the theory which predicted with amazing accuracy the intricate line emission spectrum of hydrogen. Thus, early in the second decade of this century, the Rutherford-Bohr atom provided a sound basis for the further development of atomic and molecular physics.

In 1919, Rutherford produced the first atomic disintegration when he directed energetic alpha particles along a tube containing nitrogen gas and observed a penetrating ray. This proved to be the high energy protons emitted when nitrogen atoms are transmuted into an isotope of oxygen.

In 1932, two students of Rutherford's—

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* Presented as the George W. Holmes Lecture of the New England Roentgen Ray Society on May 18, 1963.

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Cockcroft and Walton—produced the first completely artificial disintegration of an atomic nucleus. In this famous experiment, they bombarded lithium with protons accelerated by a 300 kv. machine. One proton in several million would score a nuclear hit. The two helium nuclei thus produced would recoil from each other with 17 million electron volts of energy. The measured loss of nuclear mass in this reaction exactly confirmed Einstein's prediction in 1905 of the equivalence of mass and energy.

In the year 1932, Chadwick identified a new fundamental particle—the neutron. This uncharged particle, slightly heavier than the proton, was destined to be the key to the large-scale release of nuclear energy. In 1932, the Curie-Joliot team induced the first artificial radioactivity by bombarding aluminum with alpha particles producing radiophosphorus. Soon to follow were the fission of uranium by slow neutrons, the first nuclear reactor, the atomic bomb, the thermonuclear bomb, and now the generation of electric power from nuclear sources.

ROUND HILL 5 MILLION VOLT GENERATOR

Let me return again to the New England scene. Van de Graaff and his MIT associates had assembled a large air-insulated belt generator in a blimp hangar on the estate of Col. Green in New Bedford, Mass. (Fig. 1). By 1933 this now famous electrostatic generator had reached new voltage heights, over 5 million volts between terminals. A few years later it was moved to Cambridge and rearranged with vertical acceleration tubes. For the next 15 years, this apparatus accelerated beams of monoenergetic positive ions and electrons for precision studies of nuclear energy levels and for investigating the interactions of electrons and x rays with matter. Today nuclear structure research is being pressed all over the world by ever more powerful descendents of this original machine.*

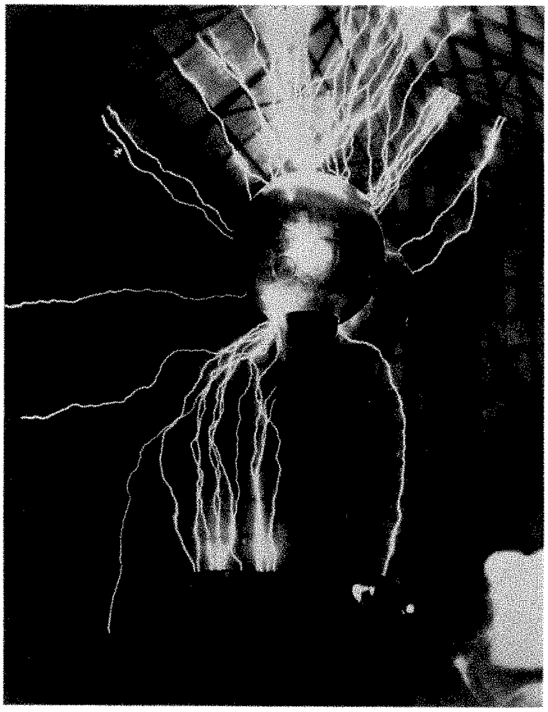

Fig. 1. Original Van de Graaff electrostatic belt generator in a sparking demonstration at Round Hill, Massachusetts, in 1932.

WE DEMONSTRATE THE POWER OF ELECTROSTATICS

In 1934, under the stimulating influence of Robert Van de Graaff, I was continuing post doctorate studies in Electrical Engineering on the voltage-insulating properties of high vacuum. The apparatus in my laboratory included a just-completed 700 kv. Van de Graaff generator with 1 ma. current capability and a steel high-vacuum chamber surmounted by a 700 kv. air-to-vacuum bushing.

Dr. Dresser brought over a bulbous glass x ray tube, then standard for 200 kv. therapy. We soon had the anode connected to the high voltage terminal of the generator. The cathode was held at ground potential and heated to a modest electron emission by a storage battery set on the laboratory floor. As the generator voltage was raised in the darkened laboratory, the hissing of corona could be heard. Then came ominous crackling sounds. Suddenly a bright discharge flashed from one end of the tube to

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* The large air-insulated electrostatic generator is now operating as the high voltage source for the Elihu Thompson Theatre of Electrical Science at the Boston Museum of Science.

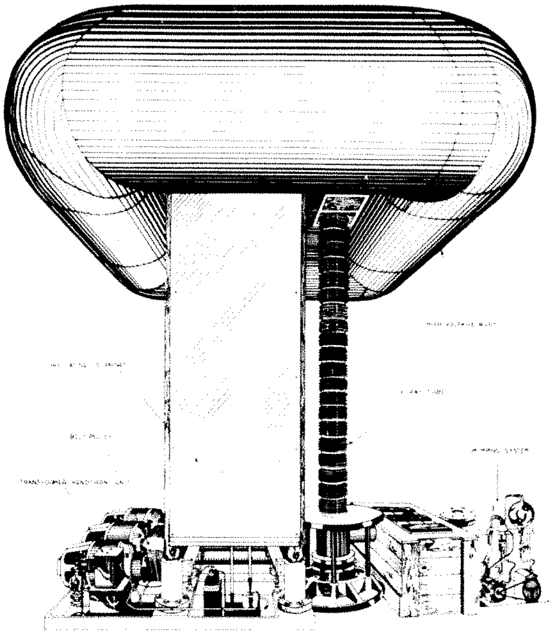

Fig. 2. Sketch of Huntington Hospital 1 million volt x ray generator.

the other. This threat to the tube and the appearance of a dull glow from the anode terminated the demonstration. Though impressed by the high voltage and the hot anode, Dr. Dresser needed evidence of actual x ray output.

A more elaborate experiment was then planned. Our steel vacuum chamber with its high voltage porcelain bushing was provided with a cathode and a water-cooled platinum anode. One Sunday morning, in May 1935, this system was demonstrated to a select scientific audience—Dr. Karl T. Compton, president of MIT and staunch supporter of scientific research including electrostatic accelerators for nuclear science, Dr. Vannevar Bush, who in the war years was to head the Office of Scientific Research and Development, Dr. Robert Van de Graaff, Dr. D. L. Webster, Prof. of Physics at Stanford University, and Dr. J. Cramer Hudson, radiation physicist at the Huntington Memorial Hospital. J. Cramer Hudson had been an assistant of Prof. William Duane and was my predecessor in the radiation physics course sponsored annually these many years by the New England Roentgen Ray Society.

Dr. Hudson had come provided with a Victoreen instrument. It was my first experience with this now ubiquitous instrument. On that beautiful Sunday morning the inadequate radiation shielding was hastily reinforced by some lead bricks near the target. Removing ourselves as far as possible from the radiation source, several measurements of x-ray output were then attempted. The first two short runs discharged the Victoreen ionization chamber at 50 cm. The third, one-half minute in duration, gave nearly a full scale 25 r reading. A fourth run confirmed the third. The fifth showed good penetration through $\frac{1}{2}$ inch of lead. Everyone was convinced that we were witnessing an unprecedentedly high and penetrating output and that we better stop while we were still intact. This demonstration supported Dr. Dresser's appeal to the Godfrey M. Hyams Trust for $25,000. Subsequently granted to the Harvard Medical School, it covered the cost of both the million volt x ray source and its building extension at the old Huntington Memorial Hospital.

HUNTINGTON HOSPITAL MILLION VOLT X RAY GENERATOR

I will pass lightly over the trials, tribulations, and triumphs of those early years. Ably advised by Dr. Van de Graaff and assisted by Frank Schultz and Bernard Cosman, the first patient was treated with the Huntington Hospital's generator (Fig. 2) with x rays produced by 1 million volt electrons impinging on a water-cooled lead target on March 1, 1937 (Fig. 3). Within a very short time, some of the conspicuous advantages of megavolt x ray therapy became clear; higher output permitting longer treatment distances, increased depth dose with less side- and back-scattering, and a not altogether anticipated increased skin tolerance which enabled the delivery of more adequate doses through the radiosensitive skin.

OTHER MILLION VOLT X RAY SOURCES

At about this time at the St. Bartholomew Hospital in London, a new x ray source was being brought up to a million volt operation by George Innes. This had been built at the Metropolitan Vickers Company under the design of T. E. Allibone. Also, at about this time in New York the first G. E. resonance transformer developed by Charlton and Westendorp was being applied to deep x ray therapy at the Memorial Hospital. In 1937, the conventional x ray voltage had just established itself at 200 kv., several 400 kv. machines were peppered about the country, and a few higher voltage x ray sources were in use.

THE MGH 1.25 MV. GENERATOR

In 1938, acting on a joint appeal by the Massachusetts General Hospital (MGH) and MIT, the Godfrey M. Hyams Trust again supported the development of a generator in the million volt range by a $15,000 grant to MIT. This resulted in the 1.25 million volt compressed-gas-insulated Van de Graaff generator designed by Robert Cloud and myself and installed on the second floor of the George Robert White Building at the Massachusetts General Hospital (Fig. 4). Here it has remained for nearly 16 years of therapeutic work; at first under the aegis of Dr. George Holmes, then under Dr. Laurence Robbins, and then your president—Dr. Milford Schulz.

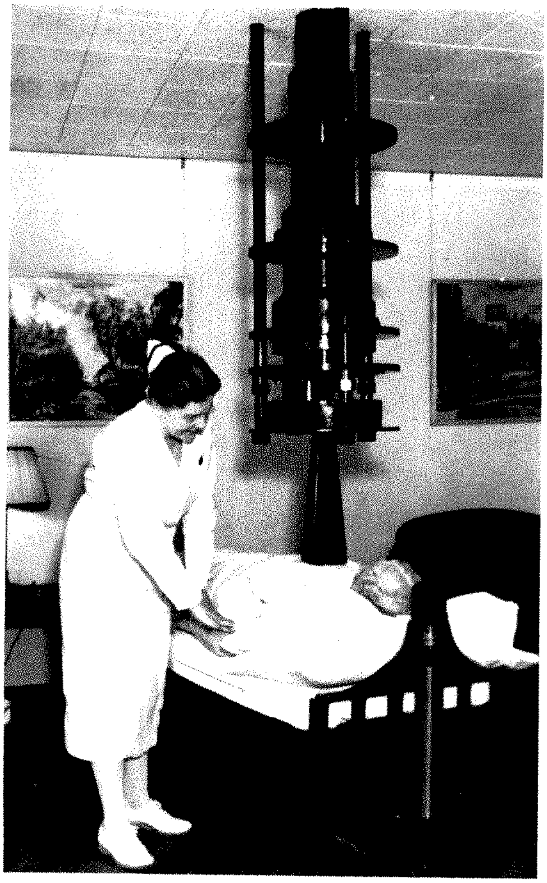
Fig. 3. Treatment room of the 1 million volt x ray facility at the Huntington Memorial Hospital.

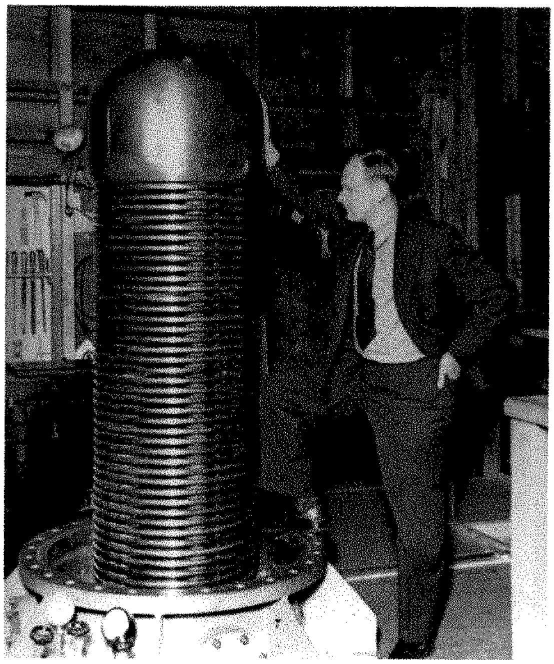
Fig. 4. Compressed-gas-insulated 1.25 mv. Van de Graaff x ray source at the Massachusetts General Hospital. Tank removed.

THE HOPE FOR SELECTIVE TUMOR ACTION

The decade 1935–45 seemed characterized by the hope that some mysterious property of megavolt radiation would increase its specific action on tumor cells. This hoped-for differential improvement, the wavelength effect, was not to be. It is now well established that the primary gain from megavolt x rays is owing to the improved dose distribution in depth rather than from a selective action on tumor. This improved distribution in depth is accompanied, however, by a beneficial reduction of absorbed dose in bone because of the inde-

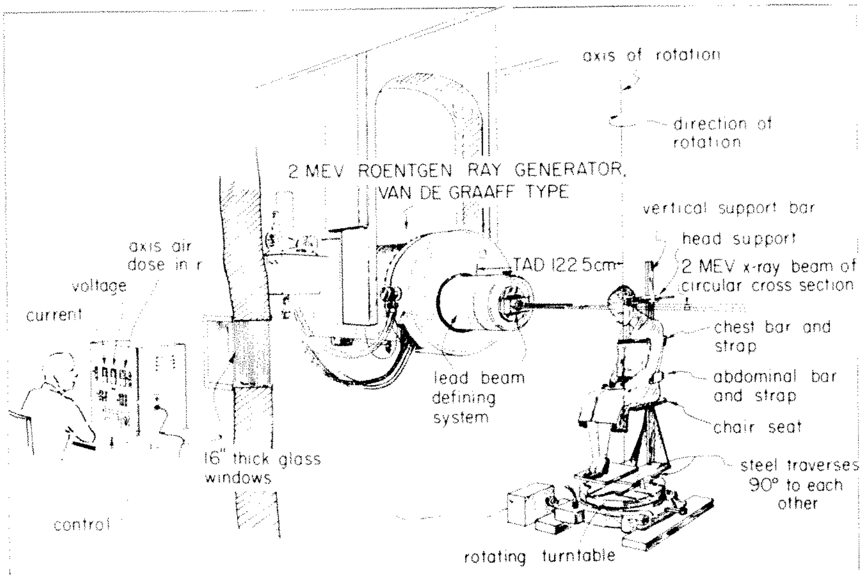

Fig. 5. Arrangement for rotational therapy of pituitary with 2 million volt pressurized Van de Graaff x ray source at the Massachusetts Institute of Technology, using circular field.

pendence of the Compton absorption process on atomic number. It includes also the increased skin tolerance which arises from the considerable tissue thickness required for electronic equilibrium.

X RAY SOURCES TODAY

In contrast with the past, the modern radiation therapist is confronted with an impressive variety of particles and radiations covering a tremendous energy range. Over 1,500 cobalt 60 sources of gamma rays, equivalent in total output to more than 3 million grams of radium or over 1,000 times the world's available supply of this precious material, are now installed for therapy throughout the world. The forty naturally-radioactive isotopes found on this planet are supplemented by hundreds of artificially radioactive isotopes, many of them with half lives and emissions peculiarly suited to specific tracer or therapeutic applications.

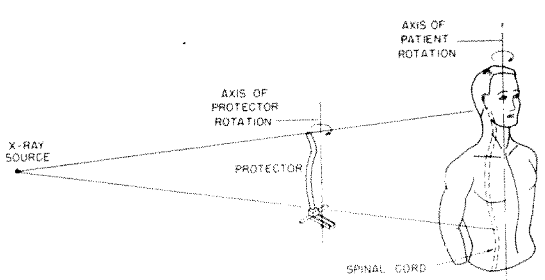

Fig. 6. Diagram showing method of protecting the spinal cord during rotational therapy with megavolt x rays.

The early electrostatic and transformer-powered x ray machines soon moved up to 2 million volt operation (Fig. 5 and 6). At this voltage x rays match almost exactly the physical and biologic properties of the gamma rays from radium and cobalt 60. The attractiveness of these machines lies in the higher beam intensity proceeding from a far smaller source. As Sir Brian Windeyer has remarked, the 2 megavolt x ray sources were the workhorses of supervoltage therapy during the past decade.

These more favorable radiations placed a higher value and stress on the radiotherapist. The ability to deliver a more adequate dose, to include regions of actual or potential spread, to protect uninvolved or radiation-sensitive structure, to reduce patient reaction, all obviously increase the requirement on clinical knowledge and judgment. For the physician radiation therapy becomes more interesting and challenging—and often more rewarding.

Today, indirect accelerators—betatrons, electron synchrotrons, and microwave linear accelerators—offer x rays of still higher energy. Four, 6, 8, 20, 35, 50, and 70 million volt apparatus are available or technically feasible.

This is not the time or place to argue the question of optimum x ray energy. That too much voltage may be as undesirable as too little is evidenced by a voluntary return from 70 mev. x rays toward the lower energies. The lower end of the megavolt x ray scale is characterized by less exit skin reaction, less absorption in bone by the pair production process, an inherently broader beam for the treatment of regional as well as localized fields, and greater simplicity of apparatus. For x ray therapy I feel the range from 2 to 20 mev. makes physical as well as radiologic and clinical sense. My personal preference lies nearer to the lower figure.

ELECTRON THERAPY

Electrons themselves, directly applied to tumor-involved tissue, are becoming the current fashion in radiation therapy. Recognized by physicists and studied as "cathode rays" even before Roentgen's famous discovery in 1895, identified as tiny swiftly-moving negatively-charged particles by J. J. Thomson in 1898, electrons have required all this intervening time to reach the threshold of availability for therapeutic use.

I can remember the caution and excitement with which Robert Cloud and I first peered at the electron beam issuing from the 1.25 mv. Van de Graaff accelerator. This was one night in 1939, some months before the machine was delivered to the Massachusetts General Hospital. We had replaced the x-ray target with a thin aluminum window and placed ourselves beyond the calculated 5 meter maximum range in air of such electrons, accepting the stopping-power of some intervening paper wall board as additional insurance against these potent particles.

In the darkness of MIT's old wooden hangar, a relic of World War I, the soft violet luminosity evoked by interactions of the energetic electrons with the air molecules was deceptively beautiful. From a safe distance we observed the diverging luminous beam fading off in intensity as it approached the floor. Again and again we watched the interesting change in the angle of divergence as the voltage was lowered and raised. Before the machine left the MIT scene, we had measured the distribution of ionization in depth of water, aluminum, copper, and lead. Earlier investigators had noted many of the interesting effects of cathode rays. We noted and measured some of our own, and began thinking of the advantages which the localized subcutaneous distribution of electron dose might offer for the control of superficial disease.

It is therefore with very real appreciation that Kenneth Wright and I look back at the opportunity for clinical investigation of electrons which Dr. Hugh Hare and Dr. Magnus Smedal and their Lahey Clinic associates have provided. Our first electron therapy patient in 1951 was a 76 year old man with mycosis fungoides, finally rampant after years of control. He was dramatically benefited for 4 more years by this new procedure. Over 1,700 treatment series have since been given at MIT with electrons, many of them to patients with very extensive disease. Last year Dr. Ferdinand A. Salzman summarized the observations of this unique program in a paper titled "Ten Years Experience with Low Megavolt Electron Therapy." During this entire period the Damon Runyon Memorial Fund for Cancer Research supported these physical and clinical studies with high energy electrons at MIT.

ELECTRONS FOR DEEP THERAPY

Meanwhile and elsewhere, interest has been growing in the application of electrons of much higher energy to the deep tumors now commonly treated by penetrating x rays. For the thicker body sections, deep electron therapy may require electron energies up to 50 megavolts. The two pre-

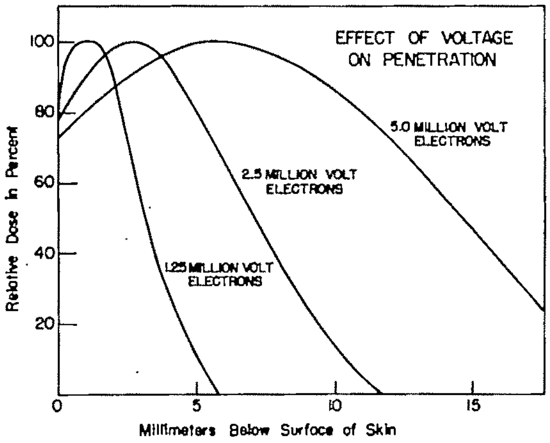

FIG. 7. Dose distribution in depth of tissue produced by normally incident 1.25 mev., 2.5 mev., and 5 mev. electrons.

ferred sources for electrons of such energies are: (a) the betatron, a circular electromagnetic accelerator first reduced to practice in 1940 by Dr. Donald Kerst of the University of Illinois, and (b) the microwave linear accelerator or Linac, a World War II radar by-product which accelerates groups of electrons in a straight-line path along a special copper waveguide fed by pulses of very high frequency power.

Whether such energetic electron beams will prove equal or superior to megavolt x rays for the management of deep tumor problems is an interesting question. If they do, it will be solely because of the different distribution of dose in depth of these light particles (Fig. 7 and 8) as compared with x rays. Such electrons have a linear energy transfer (LET) closely similar to that of x rays produced at the same energy. Electrons, being the lightest charged particle of nature, are more easily scattered by the skeletal structures than x rays. Thus the dose distribution by electron beams may prove more difficult to control in deep tumor work than with penetrating x rays. Very penetrating electron beams can, like x rays, produce reactions at the exit skin. Nevertheless, it is already clear that electrons have considerable promise for superficial and subcutaneous tumors and it is reasonable to believe that important supporting roles to deep tumor x ray therapy will also be found for them.

THERAPY WITH HEAVY PARTICLES

And what of the nuclear particles of nature? The protons, neutrons, alphas, and perhaps even heavier nuclei accelerated by the cyclotrons, synchrocyclotrons and synchrotrons of high energy nuclear physics. What of their prospects for radiation therapy? Is their dose distribution in depth or selectivity for tumor such as to yield important clinical advantages?

Of all of these particles, neutrons are technically the most available. Energetic neutrons owe their considerable penetration to their lack of electric charge. In tissue such neutrons lose energy primarily by direct collision with hydrogen nuclei. These protons recoil to produce short densely-ionized tracks with resultant biologic effect. Being immune to electric fields, neutrons can enter atomic nuclei with little opposition. A measurable but innocuous amount of short-lived radioactivity is produced when a therapy dose of neutrons is delivered to animal tissue. Although the clinical impression gained in Dr. Robert Stone's pioneering investigation almost two dec-

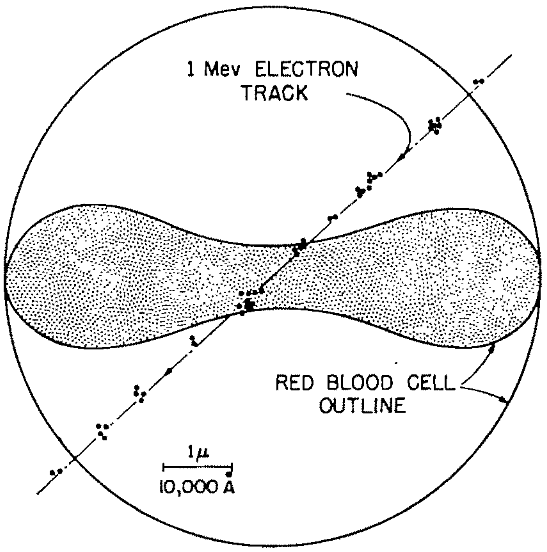

FIG. 8. Clusters of ionization along the track of a 1 mev. electron in water, superimposed to scale on the outlines of a red blood cell.

ades ago was rather unfavorable, external neutron beam therapy deserves and is likely to receive another trial.

Many nuclear transformations are induced by neutrons which have been slowed down to room temperature. The attractiveness of the principle of boron-neutron therapy lies in the high capture probability which the boron atom has for such thermalized neutrons. This boron-neutron interaction causes the emission of an energetic alpha particle which almost certainly will destroy the cell in which it originates. But the selective absorption of boron compounds by tumor cells and the distribution in depth of a slow neutron gas issuing from a reactor port still leave much to be desired.

Energetic heavy particle beams from synchrocyclotrons are in medical use at the University of California Radiation Laboratory in Berkeley and more recently at the Harvard Cyclotron Laboratory here in Cambridge. With utmost ingenuity and precision, these proton and alpha particle beams are being directed toward small head targets such as the pituitary gland. These studies seek to exploit the quite definite range of such nuclear particles and their relative freedom from scatter. That their LET is hundreds of times higher than for electrons and photons, that they may be indifferent to the often low oxygen level in tumors, and that they have a narrow Bragg peak of ionization at the end of their range adds additional interest to these heavy particle approaches.

NEGATIVE PIONS AND OTHER STRANGE PARTICLES

Quite recently it has been suggested that the negative pi meson, or negative pion, may have tumor therapy possibilities. This is a particle with charge equal to that of an electron but with 276 × the electron mass. It is produced by directing high energy protons from powerful synchrocyclotrons into various target materials such as graphite or lead. Negative pions have a short life time, about 2×10^{-8} sec., but it is long enough to enable them to travel to a tumor site. At the end of its range, a negative pion may be captured by a nucleus of carbon, oxygen, or nitrogen and cause it to explode into a shower of alpha particles, neutrons, and protons. It is estimated that the tissue dose at the end of the pion range is perhaps 5 times higher than the ionization dose delivered in transit through the tissue.

But there are many problems. Negative pion beam intensity is very low even with the world's most powerful accelerators. The pion beam is not clean; it is accompanied by a background of electrons, mu-mesons, and neutrons. At this stage, the usefulness of this new particle is highly speculative, the techniques difficult, and the investment for purely medical purposes prohibitive. But science is undismayed. Since the discovery of the neutron in 1932, thirty strange new particles have been identified. Many of these are rare, all of them are difficult to produce and control. Yet we can be certain that some of them, as well as more of the 92 atomic nuclei, will one day be regarded with a speculative eye on their therapy possibilities.

QUO VADIS?

What then is in store for radiation therapy? Are we destined to go on seeking for a new ionizing agent, a better sensitizer, a deferentially selective particle, or some combination of these? Must radiation therapy inevitably progress from the simple and familiar to the complex, the unknown, the expensive, and the unattainable?

To some degree the answer to all of these questions is YES. But in the long run of time, the impractical, the excessively specialized, and the inferior will disappear. Under the pressure of human need, what will remain and advance must meet the requirements of sound radiation physics and radiobiology, applicability to a wide spectrum of tumor problems, general availability to the radiologic profession, with reasonable economics and simplicity. To me these considerations argue strongly for megavolt x rays and electrons.

The past two decades have seen the

management of malignant disease by radiation advance substantially in acceptance and in clinical performance. It still has very far to go. Much of this further progress will undoubtedly come by improving the sources we already have and, most importantly, using them with greater understanding and ingenuity. It is a task in which everyone of us can contribute.

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Cambridge, Massachusetts

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INTRODUCTION TO THE SYMPOSIUM ON PROTRACTION AND FRACTIONATION*

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EVER since Regaud's famous experiment on the ram's and rabbit's testicle in 1920, the importance of the distribution of dose in time has been recognized and investigated. The problem has been rather extensively studied, experimentally. At present there also exists much material of more or less systematic studies related to clinical observations. Coutard had already experimented with practically every possible over-all treatment time from 1 to 12 weeks; however, it was Baclesse who systematically analyzed the very large material accumulated by Coutard and by himself and demonstrated in greater detail that certain important conclusions with regard to the effect of over-all treatment and time can be drawn. Coutard also experimented with the effect of different rhythmic distributions and, in his system of periodicity, approached something similar to what we shall discuss under the term "split-course technique."

Every radiation therapist has made some observations of his own. Some of these unsystematic observations, if properly integrated, have been useful in supporting certain conclusions from more systematic studies.

It now appears timely to attempt an analysis and evaluation of the rather considerable and instructive *clinical* material; the meeting of this Society provides an ideal opportunity for such a synopsis. Sufficient data are available to permit certain clinically useful conclusions. While these are, of course, tentative, they could provide suggestions for further clinical investigation and may also influence the design of experimental studies.

When planning this symposium, I attempted to have the different aspects of the time-dose relationship presented separately. While this may be somewhat artificial, it was hoped that it would lead to a better understanding of this problem. Accordingly, in Dr. Baclesse's paper the problem of over-all duration will be discussed. The other essayists will consider the effects of different forms of rhythmic distribution of dose during this over-all duration.

The use of the terms, "protraction" and "fractionation," has been deliberately avoided. These terms have been used in different connotations and perhaps an agreement on exact terminology may soon be reached.

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HYPERFRACTIONATION*

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IN DISCUSSING hyperfractionation, a definition of the terms "fractionation" and "protraction" may be of value.

Definition of Fractionation. Fractionation means the regular distribution of the total dose of radiation over a certain number of days (over-all time). The dose may be delivered every day, every other day, or every 3 days. The distribution depends upon whether we are dealing with a single lesion irradiated through one single field or with a locally and regionally extensive lesion, irradiated by cross-firing, such as pharyngeal cancer with lymph node involvement or cancer of the breast.

As far as alteration of *normal* tissues is concerned, the following example demonstrates that daily irradiation gives a slightly increased efficiency:

A woman was treated in 1940 for an extensive lymphosarcoma of the left tonsil, without lymph node involvement. The patient is doing well after 22 years. She was irradiated with conventional 200 kv., 1.5 mm. Cu half value layer; field size 6×8 cm.; focus skin distance 50 cm. The right side received 100 r/skin every day, 32 treatments in 38 days. The left side received 200 r/skin every other day for 16 treatments in 38 days. The combined (entrance and exit) dose on the skin was approximately 4,000 r to each side.

After 22 years, the only noticeable difference is a somewhat more marked epilation on the right side, which had received daily irradiation. Hence, we may conclude that the hair follicles, the radiosensitivity of which represents a very sensitive test, have been slightly more altered on the right as compared to the left side.

This observation on normal tissue makes us feel that it can be applied to cancer tissue. We believe that irradiation to more or less extensive skin cancer given daily or every other day is the most efficient technique both for the effect on the cancer and for cosmetic result. Irradiation every three days seems to be too long an interval.

For cancer of the head and neck, the best results have been obtained with 2 opposing fields, treated alternately every other day. For breast cancer, with multiple fields (we usually use 6 fields), 2 fields are irradiated on the same day; therefore, each field is irradiated every 3 days, or twice a week.

Definition of Protraction. Protraction is the r per minute rate, or the number of r delivered per minute. As is well known, Coutard used to recommend very low r per minute rates, from 2 to 3 r. We have tried higher r per minute rates and found that with a rate of 30 to 40 r per minute (for example, for cancer of the cervix with 10 ×15 cm. right and left anterior fields) slight differences appeared (telangiectasias), but they are of so little consequence that they should not be taken into account as far as survival is concerned. With smaller fields (*e.g.*, 8×6 cm.), skin alterations are even less noticeable.

When the cobalt 60 unit is employed the r per minute may be as high as 100. It thus appears that protraction is far less restrictive than it used to be 30 years ago.

FRACTIONATION

Fractionation, or time factor, is much more important than protraction. The time factor was established on an experimental basis with Regaud's classic research on "sterilization" of the testicle of rams and rabbits (1920), the principle of which was clinically applied for the first time by Coutard to cancer of the upper respiratory and digestive tract (1922).

Figure 1 is a reproduction of a chart by Coutard, published in 1932, in which he summed up his ideas. The top part refers to a two-week over-all time; the center part to a little less than two weeks' over-all time; and the bottom part to a little more than two weeks' over-all time.

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* Presented at the Forty-fifth Annual Meeting of the American Radium Society, San Francisco, California, April 1–4, 1963. Part of the Symposium: Protraction and Fractionation; Chairman, Dr. Franz F. Buschke, San Francisco, California.

Coutard's ideal treatment at that time was deliberately aimed to produce mucosal and skin reactions ("epithelitis" and "epidermitis," or a moist reaction) within a 2 week over-all time. Later on, he extended the over-all time to 3 and even 4 weeks. This extreme limit of 4 weeks was imposed by two facts: first, the appearance of the "exudative epidermitis," extending to the whole field area and secondly, the fear of "vaccinating" the tumor (rendering it radioresistant), due to the refractory conditions which were thought to appear beyond an overlong period of time.

Figure 2 is a chart summarizing the results of clinical research on skin reaction with 200 kv. roentgen therapy. (1) The first two horizontal columns from the top show Coutard's classic method, reaching the limit in the fourth week and stopped by the moist reaction. (2) The following two columns show progressively increasing over-all time, moist skin reaction being observed at the sixth and then the eighth week, by remaining under the threshold dose. The arrows on the right pointing upward indicate the time of the appearance of the moist skin reaction, at which time treatment is terminated.

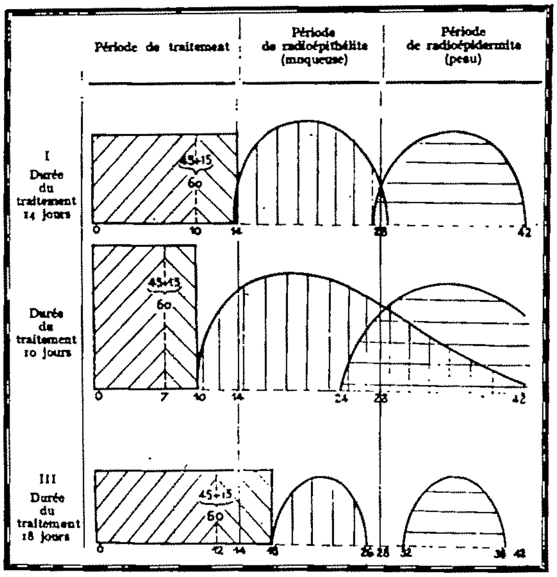

Fig. 1. Chart published by Coutard, showing the fractionation and over-all time used in his method (in *Radiophysiologie et Radiothérapie*, 1932, *2*, 85).

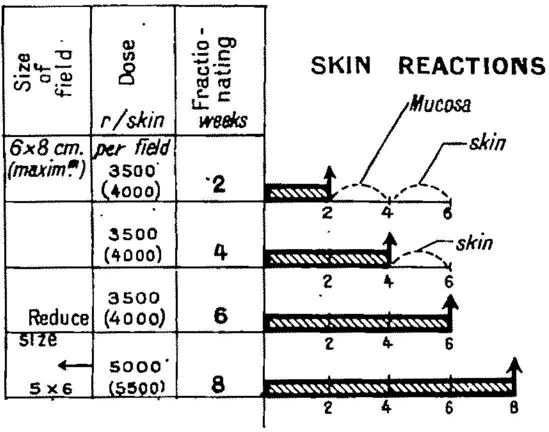

Fig. 2. Chronologic chart of skin reactions for 200 kv. therapy, in relation to doses and field sizes, showing the great variation in over-all time irradiation, determined mainly by clinical considerations (extent, histologic variety, general condition of the patient).

The important information that may be gleaned from this chart relates to (a) the chronology of the skin reaction and (b) the possibility of increasing the total dose by a factor of one-third on the average. This latter can be done in two ways: by a reduction of the field size after a certain skin dose (from 3,000–4,000 r) is reached and by irradiation through tangential fields, when possible, *e.g.*, when treating large lymph nodes in cases of head and neck cancer.

The chart demonstrates a great number of possibilities in choosing the time factor, depending upon the local and regional extension of the disease, the histologic variations, and the general condition of the patient.

Three cases of cancer of the antrum invading the suprastructures of the maxilla are briefly presented to show the importance of fractionation versus dose.

The first patient was irradiated in 1922 in an over-all time of 12 days. He developed a very severe skin reaction with deep late sequelae including blindness and died 15 years later from intercurrent disease.

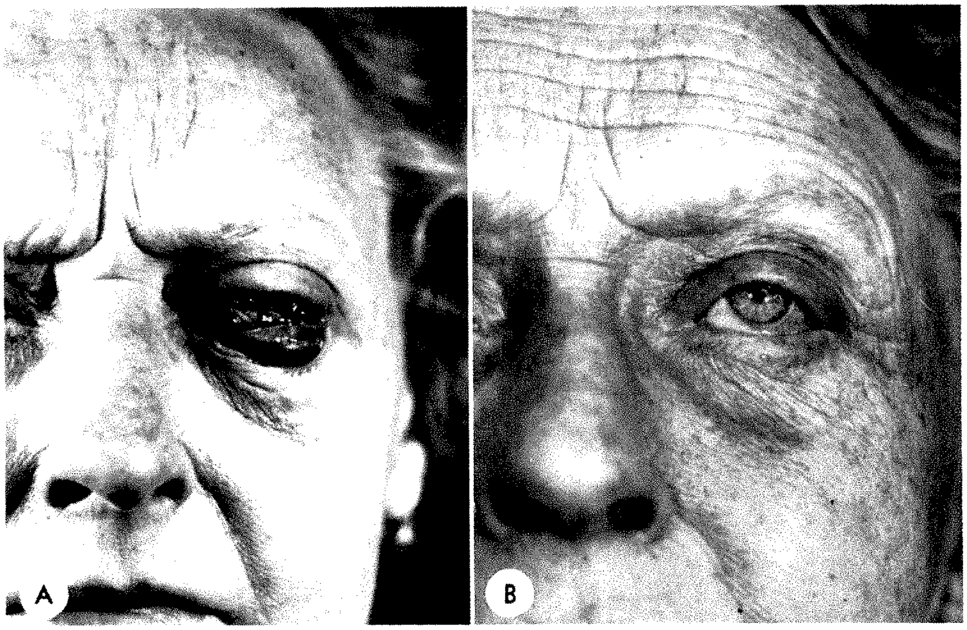

Fig. 3. Epithelioma of the suprastructure of the left antrum verified by surgical biopsy. Fractionation: 61 days (200 kv.). Mild dry skin reaction. No damage to the lens. Patient living (1963) after more than 12 years with good local result. (*A*) Before treatment. (*B*) After treatment.

The second patient was treated in 1930 in a period of 18 days with resulting severe skin reaction. The late sequelae were less marked than in the first case; however, there was cataract formation and blindness of the left eye. She died of intercurrent disease 10 years after treatment.

The third patient, treated in 1950, received a higher total dose than the 2 previous patients. With an over-all time of 61 days, only a very slight, dry skin reaction developed. There was no damage to the lens. The patient is still alive (1963) after more than 12 years, with good skin appearance and no cataract formation (Fig. 3, *A* and *B*).

Figure 4*A* likewise demonstrates the importance of hyperfractionation. This patient had an extensive infiltrative epithelioma of the inner angle of the left eye ("cancer térébrant"). He received 6,500 r/skin with 200 kv., spread over 67 days (1949). Figure 4*B* shows the eye 2 years later (1951). After 5 years glaucoma occurred, requiring enucleation of the eyeball. No cancer was found. He died from intercurrent disease 9 years following treatment, with the skin disease clinically controlled. The post-

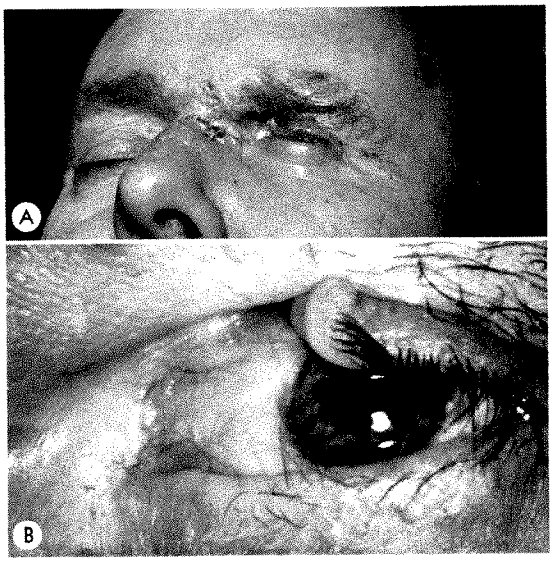

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Fig. 4. (*A*) Extensive infiltrating epithelioma of the inner angle of the eye ("cancer térébrant") treated with 200 kv., 6,500 r/skin in 67 days over-all time (1949). (*B*) The inner angle of the eye 2 years later (1951). During the fifth year (1954) enucleation of the eyeball for glaucoma was performed. No cancer cells were found. Patient died 9 years after treatment from intercurrent disease.

radiation complication (glaucoma) was unavoidable because of infiltration of both eyelids.

DISCUSSION

It appears that the 2 to 4 week over-all irradiation time may be exceeded by regularly distributed doses delivered every day or every other day; however, this can only be ascertained by a study of patients with long survival periods. To prove it, we chose the cases with extensive carcinoma of the cervix treated exclusively by conventional 200 kv. roentgen therapy from 1930 to 1946. Of 100 cases, 23 lived from 6 to 32 years after treatment (Table I). The number of survivals in the first 2 columns of Table I is significantly lower than in the last 3 columns. At the same time, the damage (to skin, rectum, and bladder) was more marked in the cases of the first 2 columns, and greatly diminished in those of the last 3 columns.

Thus it may be said that hyperfractionation with high total doses allows control of advanced cancer, including sometimes the so-called radioresistant tumors, such as cylindromas of the salivary glands. It also allows preoperative irradiation with high total doses.

HAZARDS

The 2 to 4 weeks fractionation with high total doses produces marked skin reactions and may lead to late sequelae, such as radiation-induced cancer, as illustrated by the following 2 examples.

Table I

FRACTIONATION IN 23 OF 100 CASES OF ADVANCED CARCINOMA OF THE CERVIX SURVIVING 6 TO 32 YEARS

(Treated by 200 kv. roentgen therapy alone from 1930 to 1946 at the Curie Foundation)

Fractionation Period (wk.)	No. of Patients Surviving
4	1
4–6	2
6–8	5
8–10	8
10–12	7
Total	23

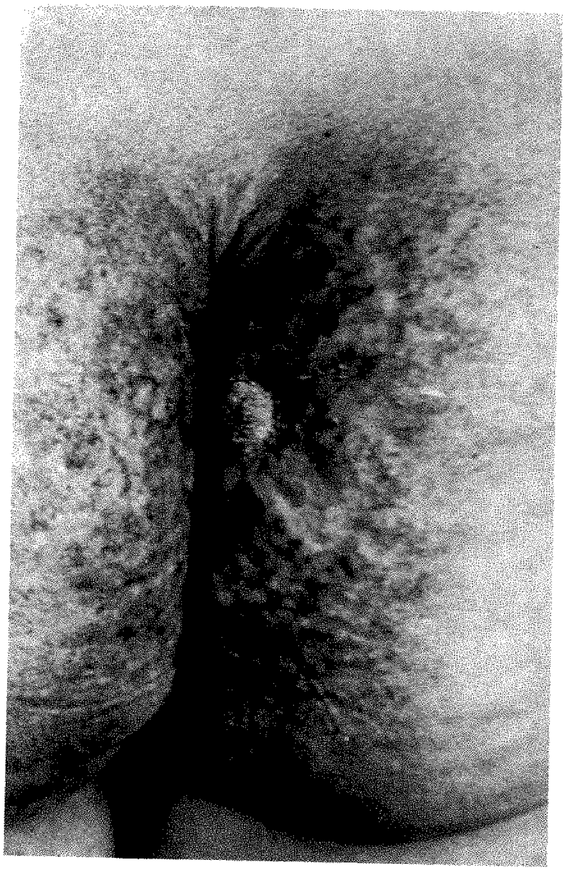

Fig. 5. In this patient, a papilloma developed 3 years after 200 kv. roentgen therapy for carcinoma of the cervix in 32 days over-all time. She died 15 years after treatment from intercurrent disease and the papilloma, which had increased in size later, was still present.

Observation I. A patient with cancer of the cervix was treated in a 4 week period (32 days over-all time) with resulting moist skin reaction of the posterior gluteal fields followed by late skin alterations. A papilloma appeared 3 years later at the site of the bleeding area in the center of the moist skin reaction (Fig. 5). Fifteen years later when the patient died from intercurrent disease, the papilloma, which had increased in size, was still present.

Observation II. A 54 year old woman was treated in 1933 in a 4 week period at a rate of 4 r/minute for an undifferentiated epithelioma of the nasopharynx and a 5×3 cm. hard, fixed lymph node on the right side of the neck. A very severe moist skin reaction followed. Three

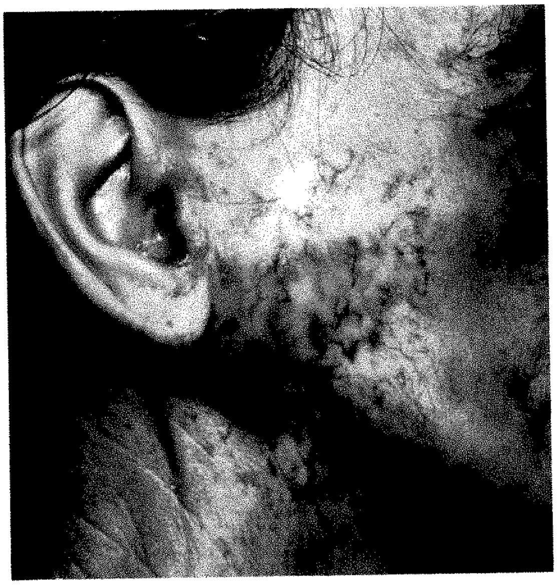

Fig. 6. Patient was treated for an epithelioma of the nasopharynx with lymph node involvement. Fifteen years after treatment a radiation-induced cancer of the right external auditory canal developed which caused patient's death 1 year later. There was no evidence of recurrence of the nasopharyngeal cancer.

years later (1936), she developed skin necrosis, then bone necrosis of the right antrum. Fifteen years later (1948), a radiation-induced cancer of the external auditory canal developed. After 1 year (1949), she died from this very painful cancer, although she was clinically cured of the nasopharyngeal cancer and the lymph node involvement (Fig. 6).

Such late hazards may be avoided by using hyperfractionation. At least we have never observed any skin cancer in patients with long survival times. We believe that this is due to the hyperfractionation with limited fields, in spite of higher total doses and higher r per minute rates.

COBALT 60 TELETHERAPY

We do not feel that the use of high energy radiation, such as cobalt 60 gamma rays, has fundamentally modified the fractionation principle with limited fields. However, after 6 years' experience with cobalt 60 beam therapy, we believe that the *total dose* may be increased by one-fourth to one-third on the average and that the *fractionation* may be reduced by the same one-fourth to one-third factor. We do not think that a short over-all time (2 to 4 weeks) can be used for cases with extensive involvement, such as pharyngeal cancer with large lymph nodes or breast cancer.

CONCLUSIONS

The hyperfractionation method, with high total doses, has the following advantages:

1. Besides the direct cellular action, there certainly exists an action on the surrounding vasculoconnective tissues which has very important consequences in the postirradiation period. This fact is well proved by late resorption of certain tumors, sometimes occurring long after treatment, and is the main cog in the rationale of hyperfractionation with high total doses.

The *high total dose* is necessary for the control of the cancer cells which are sometimes radioresistant. The *hyperfractionation* is necessary to preserve the surrounding tissue, the protection of which is essential from the radiobiologic point of view.

2. With this method much better results are also obtained when preoperative irradiation with high doses is given. This is especially true if high energy radiation, such as cobalt 60 teletherapy is used.

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SPLIT-COURSE RADIATION THERAPY IN MALIGNANT TUMORS*

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THE split-course technique is applied to patients treated by roentgen therapy, mostly at 250 kv., and may be defined somewhat arbitrarily as a planned course of irradiation directed to the same tumor bearing location, which is deliberately interrupted by one or more rest intervals of not less than 1 week and not more than 2 months. In general, the method is to deliver equal dose fractions on a 5 day a week basis. Lately, 3 fractions per week have been used. Logically, the general principles of the method could include techniques of treatment by several large single fractions or by combinations of radium and roentgen radiations, separated by similar intervals.

Similar methods of divided dosage were used by Holzknecht in Vienna in the 1920's, and were advocated by Coutard[5] in 1935. In 1939, Friedman and Rosh[7] gave a detailed description of periodicity in the radiation reactions of skin and mucosa, and on the basis of these observations, they suggested a split-course type of technique for the more resistant tumors. Scanlon[14] has been using a similar technique for several years at the Mayo Clinic and is an enthusiastic advocate of the method.

Earlier workers labored under the handicap of imprecise dosimetry and inadequate apparatus. The handicap of the extreme difficulty of evaluating a technique through clinical results because of the great variation in clinical material, the impossibility of a control in most cases, and the length of time needed before success can be determined is also present. Only recently important advances in radiobiology are providing us with some of the guidance which is needed in devising optimal techniques.

In my experience split-course therapy was prompted originally by the wish to spare frail and elderly patients with advanced mouth and throat cancers the severe discomfort caused by high dose therapy when given in continuous daily fractions. The so-called palliative treatment with tumor doses low enough to avoid painful local reactions gave such short-lived relief as to be virtually useless, and furthermore tended to discredit radiation therapy as a futile method of treatment. Overambitious treatment, on the other hand, often simply aggravated the patients' suffering and even hastened their demise. Although cobalt 60 beam and megavoltage roentgen therapy spared patients the distress of skin reactions, mucosal reactions could still be troublesome, and experience has shown that serious high dose complications often followed later, especially if treatment to large areas were given too fast.

In 1953, when this study was initiated, megavoltage apparatus was not available in Wales, and this was an added incentive to seek other ways of overcoming the therapeutic dilemma. It soon became apparent that by stopping treatment when local reactions were commencing, these reactions rapidly cleared up; treatment could be resumed 2 to 4 weeks later, and a respectable tumor dose could be delivered before reactions reappeared. The patient thus had only two short periods of minor discomfort which he was able to tolerate; relief of symptoms and a noticeable shrinkage of the tumor nearly always took place during the rest interval. Psychologically, this was preferable to the more protracted ordeal.

At first, the method was limited to advanced cases where only palliation could be hoped for. Later, because of the satisfactory results, it was extended to cases receiving radical therapy with the possibility of a cure. The method has been further extended by splitting treatment into 3 or even 4 parts, with 2 or 3 rest intervals, to deliver very much higher tumor doses than could possibly be given by orthodox continuous techniques in an attempt to control more advanced cases. In this way it is possible to administer doses of 7,000 r–9,000 r to the skin (with orthovoltage apparatus) without producing more than transient soreness and dry desquamation. Mucosal reactions are correspondingly mild and mucositis lasts only a few days.

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* Presented at the Forty-fifth Annual Meeting of the American Radium Society, San Francisco, California, April 1–4, 1963. Part of the Symposium: Protraction and Fractionation; Chairman, Dr. Franz Buschke, San Francisco, California.

At present the main indications for using the split-course method are: (1) where a relatively large area or volume of the body has to be irradiated with the likelihood of disagreeable local reactions, and (2) where there appears to be a need for a very high tumor dose.

Two critical questions arose during this trial. First, would splitting the treatment in this way so reduce the effectiveness of the total dose given as to negate the apparent advantages? Second, would the divided method of dosage have some adverse late effect on the vitality of the normal tissues, and be followed by a raised incidence of late necrosis?

Since this work began, some interesting advances in radiobiology have been made, which on the whole give grounds for reassurance on these points; however, only by actual clinical experience can conclusions be made. So far, my work can only be regarded as a pilot study, and dogmatic conclusions are not justified. Many of the earlier cases were so advanced or elderly that few long survivals could be expected. Also, only recently has the split-course method been used to deliver extra high dose radiation. Nevertheless, I believe that, insofar as patients and doses have been comparable, the results with the split-course method do not appear to have been worse than would be expected with continuous treatment to the same dosage. Complications such as necrosis of laryngeal cartilage have occurred after split-course therapy, but on the other hand, several advanced cases of laryngeal cancer, where laryngectomy was refused, have been healed without incident and with recovery of a good voice. Skin changes, many years after split-course therapy, are decidedly less pronounced than those following similar or smaller doses given by continuous technique.

In the few cases where a control was possible, by dividing the tumor into separate segments and treating one part by the split and the other by the orthodox method (same fraction size and total dose), the results have been equivocal. Five cases of epithelioma of the skin, 1 of recurrent breast cancer and 1 of epithelioma of the jaw have been so treated. In 2 cases of advanced skin cancer, the tumor recurred in both areas; in the other 3 cases, it has remained controlled in both areas. In the case of recurrent breast cancer, the result was indeterminate—there has been some induration in both areas at 6 months. In a case of epithelioma of the jaw (reported in 1962[12]), there was an apparent advantage when the split-course method was used.

Table I shows the type of cases treated from 1953 up to the end of 1959 and previously reported[12] as well as the more recent cases treated from 1960 through 1962. The results of treatment in the patients treated from 1960 through 1962 are shown in Table II. Here, of course, few patients are available for more than a 2 year assessment.

Some changes have been made in the method of presenting results. A period of 6 months of apparently complete control of disease within the treated area is considered the least that can be regarded as significant. Even this can only be regarded as an indication of useful palliation. To collect a reasonable number of 5 year results with predominantly elderly patients with carcinoma of mouth, pharynx and larynx requires a long period. Several of the earlier patients, whose tumors were successfully controlled, died from intercurrent disease, thus limiting the period available for assessment.

Table I

CASES TREATED BY SPLIT-COURSE ROENTGEN THERAPY (1953 THROUGH 1962)

Site of Tumor	1953–1959*	1960	1961	1962	Total
Tongue, Mouth and Tonsil	28	3	7	5	43
Laryngopharynx (pyriform fossa and epiglottis)	21	7	11	7	46
Intrinsic Larynx (glottis)	12†	—	8	8	28
Postcricoid and Upper Esophagus	17	1	3	4	25
Nasopharynx	3	—	1	—	4
Lung (bronchus)	9	7	12	14	42
Breast (preoperative or recurrent)	3	4	5	4	16
Sarcoma (various)	—	4	3	7	14
Abdominopelvic (various)	—	2	1	2	5
Skin (squamous cell epithelioma)	1	—	5	1	7
					230

* Previously reported.[12]
† One case missed in report.[12]

Since the method has been increasingly used in cases of inoperable carcinoma of the breast and lung, younger patients are treated, but the distressingly high mortality from distant metastases, often occurring within a year or so of treatment to the primary site irrespective of local control is a discouraging factor.

It was tempting to classify cases as palliative or radical since many cases were hopeless from the beginning; however, to make the assessment somewhat more stringent, all patients who could not be evaluated at least 6 months after treatment, even though the tumor had been controlled, were placed in the indeterminate group, while

Table II

RESULTS OF SPLIT-COURSE THERAPY (1960 THROUGH 1962)

(Neoplastic disease clinically evident before treatment in all cases—biopsy proved in 90 per cent)

Site of Primary Tumor	Effect on Primary Disease and Metastases within Treated Area							Per Cent of Determinate Cases Controlled 6 months
	Controlled throughout Period of Observation				Persistent	Recurrent	Indeterminate	
	6 months+	1 year+	2 years+	3 years				
Mouth, Tongue and Tonsil	5	4	1	1	3	2	5	50
Laryngopharynx (pyriform fossa)	8	6	4	—	3	6	8	47
Intrinsic Larynx	10	7	5	3	1	—	6	91
Postcricoid	1	1	—	—	1	1	5	33
Lung (bronchus)	7	6	1	—	4	8	14	37
Breast (inoperable or recurrent)	—	—	—	—	8	1	5	—
Sarcoma (various)	6	4	1	—	2	1	5	67

Controlled = Clinical disappearance of all neoplasm within the treated area.
Persistent = Clinical or pathologic evidence of growth in treated area after treatment.
Recurrent = Recurrence at any time after treatment within the treated area.
Indeterminate = No clinical evidence of recurrence, but period of observation less than 6 months:
(1) Patient treated less than 6 months ago.
(2) Patient died before lapse of 6 months from treatment (any cause).
(3) Not examined within 1 month of death and no postmortem examination done.

Table III

ANALYSIS OF CASES OF CARCINOMA OF BREAST

Case No.	Size and Extent of Tumor	Treatment Factors	Disease in Treated Area	Duration of Observation	Clinical Status
1	Fixed mass 5×4 cm. Multiple skin nodules. Axillary lymph nodes +	10×300 r—66— 8×300 r=5,400 r	Persisted	11 months	Died of thoracic metastases
2	Outer half of breast. Skin nodules. Axillary lymph nodes +	12×200 r—20— 9×230 r=4,470 r	Persisted	2 months	Died of stroke
3	Tumor 3×4 cm. Lymph nodes + in axilla and supraclavicular region	10×250 r—34— 9×250 r=4,750 r	Simple mastectomy 6 months after treatment. Scirrhous carcinoma present in sections		Died of metastases and local recurrence 10 months after operation
4	Recurrent nodules after mastectomy and 20×200 r irradiation	10×300 r—25—10×300 r=6,000 r	Clinically controlled	4 months	Died of lung metastases
5	Fixed tumor 6×7 cm. Axillary lymph nodes +	10×200 r—31—10×225 r 31—10×250 r=6,750 r	Simple mastectomy 2 months after irradiation. Dense fibrosis, a few rare clusters of cancer cells present in sections		Died of metastases after 18 months. No local recurrence
6	Fixed tumor 4×5 cm. Axillary lymph nodes clear clinically	15×200 r—18—12×250 r 8×300 r=8,400 r	Mastectomy 4 months later. Section: very fibrotic tissue, but some apparently viable cancer cells seen		Alive and well 1 year after treatment
7	Fixed fungating mass 9 cm. in diameter. Axillary lymph nodes +	10×300 r—28—10×300 r=6,000 r	Indeterminate. Marked shrinkage at 2 months		Died of metastases after 2 months
8	Fungating mass 8 cm. in diameter. Axillary lymph nodes ++	10×300 r—24— 5×500 r=5,500 r	Tumor disappeared, but recurrence developed 4 months after treatment		Died of metastases
9	Multiple recurrent nodules after mastectomy	8×400 r—27— 8×400 r=6,400 r	Convalescing at present, but only 2 months after treatment		Alive and well
10	Diffuse tumor 6 cm. in diameter. Axillary lymph node 7×5 cm.	12×250 r—21— 4×250 r 6×250 r—13—10×250 r=8,000 r	Mastectomy 2 months after treatment. ? Viable cancer cells seen in sections (skin reaction only first degree)		Alive but has bone metastases
11	Fixed growth 3 cm. in diameter	6×500 r—28— 6×500 r=6,000 r (given 3 times a week)	Mastectomy 5 months after treatment. Marked fibrosis but viable cancer cells also present in sections		Alive and well 18 months after treatment
12	Tumor 10×12 cm. invading skin	10×300 r—25—10×300 r=6,000 r	Mastectomy 3 months after treatment. Large areas of hyaline fibrosis, but cancer cells still present in sections		Alive and well after 3 months
13	Fixed tumor 6 cm. in diameter. Axillary lymph node 4 cm.	11×300 r—60—10×400 r=7,300 r	Tumor and enlarged lymph node shrinking. Only treated 2 months ago		Alive and well
14	Fixed tumor 5 cm. in diameter. Axillary lymph nodes+	9×400 r—45—11×400 r=8,000 r	Tumor and lymph nodes almost undetectable. Only treated 2 months ago		Alive and well

recurrence at any stage put the patient into the recurrent category, even though control may have lasted several years.

A more detailed analysis of the carcinoma of breast cases is of interest (Table III) because many were initially inoperable, but after irradiation mastectomy usually became possible. This provided interesting histologic material for examination. It will be seen that in no case did the radiation treatment completely eradicate microscopic evidence of cancer. It may be debated whether these surviving cells were in fact viable, but their presence in a specimen removed 5 months after irradiation suggests that they still retained reproductive integrity—even if their growth rate was greatly slowed. Although this is disappointing as regards the efficacy of the treatment as a sole curative method, nearly half these patients are alive and well at the time of writing. Skin reactions were notably mild and no serious delay in healing occurred after operation.

Some long term results based on follow-up of patients treated before March, 1960 are given in Table IV. This shows that split-course therapy is compatible with long survival—and without serious complications attributable to the treatment.

The dose time factors are summarized in Table V but it is difficult to draw conclusions from them. Only a compilation of average values in controlled cases as well as in failures is given. This averaging tends to iron out interesting individual cases and does not show a significant recent trend; *i.e.*, a tendency to administer fewer larger fractions in each part and to employ 3- or 4-part courses in order to give higher doses.

Local reactions are summarized in Table vi.

In describing the dose time factors, it is essential to define the size and number of fractions, as well as the cumulative tumor dose. This is because small fractional doses are relatively less efficient than large ones in terms of cell sterilizing effect because of the gradual build-up of effect at the beginning of irradiation and the fading of latent sublethal damage between fractions given at 24 hour intervals (or longer).

This effect of fractionation is further influenced by oxygenation at the time of irradiation.[18] Since it is certain that in any but the smallest tumors a proportion of cells will be seriously hypoxic due to inadequate blood supply,[2,8] the adopted method of fractionation may well assume critical significance in clinical practice. The relative sparing of hypoxic tumor cells will be further augmented the more radiation is fractionated, and the smaller the fractions the greater the loss of efficiency in this respect (Fig. 1).

The logical way to overcome hypoxia in tumor cells would be to irradiate patients, especially those with large tumors, in a pressure chamber with 3 or 4 atmospheres pressure of oxygen.[2] This, however, is somewhat costly and laborious; compression and decompression take a long time, and there are additional problems of set-up and beam direction, and even psychologic stresses to consider. The problem of hypoxia may be partly overcome by using a split-course technique. In 1960 Cater and Silver[1] have shown by means of delicate electrodes inserted into (human) tumors that a marked rise in oxygen tension occurs in previously hypoxic regions after a course of irradiation. This is apparently due to the vascular reactions following irradiation, and perhaps also to suppression of metabolic activity in the tumor cells themselves.

Table IV

SOME LONG TERM RESULTS

(Patients treated prior to March, 1960)

Site of Tumor	Disease Controlled	
	3 Years+	5 Years+
Mouth, Tongue and Tonsil	6	4
Pyriform Fossa, etc.	6	3
Intrinsic Larynx	7	2
Nasopharynx	3	—
Lung (bronchus)	1	1
Postcricoid	1	—
	24	10

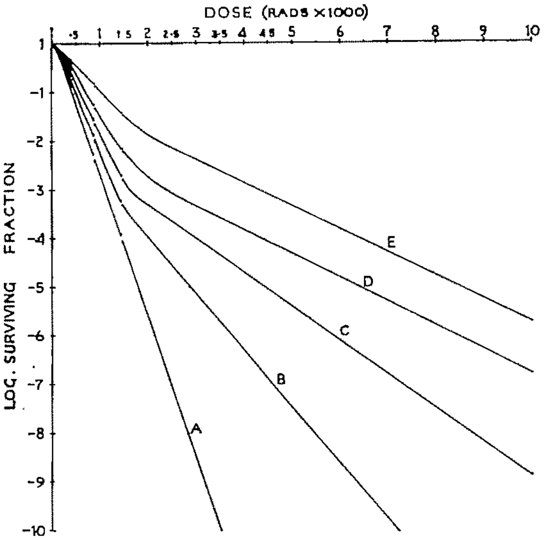

Fig. 1. Theoretic cell survival curves showing combined effect of fractionation and hypoxia. (A) Single doses; fully aerobic conditions. (B) Single doses; 1 per cent of cells anoxic. (C) 500 rad fractions; 1 per cent of cells anoxic. (D) 250 rad fractions; 1 per cent of cells anoxic. (E) 250 rad fractions; 10 per cent of cells anoxic.

Split-course therapy may usefully exploit this process, and the tumor shrinkage during the rest interval should further improve circulation in residual tumor tissue by reduction of tissue tension. One may even utilize theoretic dose response curves for mixed aerobic and anoxic cell populations (Fig. 1) to choose the best point at which to split the course. It will be seen that the slope of these curves begins to flatten out at about 2,000 rads—after which anoxic cells dominate the picture. If a rest interval is introduced after about 2,000 rads has been given, vascular reactions may be expected to restore these cells to a more aerobic state after 2 to 4 weeks; then, when irradiation is resumed, a steeper dose response should again ensue. There is some evidence from clinical fractionation data that some such improvement in oxygenation, giving a steeper dose response slope, does, in fact, occur during the course of fractionated irradiation even with continuous treatment.[6] These theoretic curves may therefore be unduly pessimistic for *in vivo* conditions, but the split-course technique would be expected to exploit this mechanism further.

The really crucial theoretic argument in favor of the split-course principle rests on the consideration of cell population kinetics. The fundamental difference between normal and malignant tissues can be identified by the fact that the proliferative activity of normal cells is regulated by delicate homeostatic mechanisms adjusted to the needs and functions of the body, whereas the proliferation of cancer cells is governed (with rare exceptions) solely by the availability of nourishment and is potentially unlimited. The regulation of normal cell populations requires two mechanisms: a stimulus to mitosis leading to proliferation and a negative feedback to check mitotic activity once anatomic or physiologic requirements are satisfied. An individual cancer cell probably has a fixed maximal growth rate (although this may change via mutation, or polyploidy, and subsequent natural selection of the more vigorous strains), but, with the rare exception of hormone-dependent tumors, it has no natural check to proliferation except exhaustion of the nutrient supply. It is this metabolic duress which prevents continued logarithmic tumor growth *in vivo*.

The stimuli to mitosis in normal cells show functional specificity and vary in different tissues (*e.g.*, red blood cell precursors in the bone marrow respond to anoxia through the mediation of a glycoprotein

TABLE V

AVERAGE VALUES OF DOSE TIME FACTORS (1960–1962)

Site of Primary Tumor	First Part	Rest (days)	Second Part	Total Dose
Mouth, Tongue and Tonsil				
Controlled Cases (7)	9.3×252 r	20	9.6×256 r	4,670 r
Failures (5)	9.75×270.5 r	25	7.25×306 r	4,760 r
Pyriform Fossa				
Controlled Cases (9)	10.4×248 r	23	10×255 r	5,130 r
Failures (7)	10.3×258 r	26	10.7×243 r	5,275 r
Intrinsic Larynx				
Controlled Cases (11)	9.7×289 r	23	9.5×288.52 r	5,470 r
Failures (1)	9×280 r	18	9×280 r	5,040 r
Postcricoid				
Controlled Cases (3)	10.3×273 r	26	10.3×273 r	5,640 r
Failures (2)	9.5×240 r	17	14×240 r	5,605 r
Lung (bronchus)				
Controlled Cases (5)	10.4×284 r	28	15.8×222 r	6,280 r
Failures (13)	11.7×200 r	32	14.8×192 r	5,140 r
Breast				
None Controlled	10.3×300 r	34	9.7×345 r	5,915 r
Sarcoma (various)				
Controlled Cases (7)	10×201 r	29	8×207 r	3,675 r
Failures (3)	10.7×163 r	32	11×230 r	4,175 r

called erythropoeitin; myeloid precursors respond to nucleoproteins released by infection or tissue breakdown leading to leukocytosis, etc.). An important natural stimulus to proliferation in many tissues is trauma. Research at the Institutum Divi Thomae, Cincinnati, many years ago showed that cell damage and cell death evoked a powerful stimulus to mitosis in epidermal cells, and mechanical trauma, damage by ultraviolet light, or by ionizing radiations could all evoke this response.[5] Local humoral agents, named "kinins" were shown to be responsible, and the release of these and other agents is also responsible for the local inflammatory reactions following trauma or irradiation. Under the influence of the stimulus to reparative proliferation and with the plentiful blood supply due to the local vascular reaction, the intermitotic cycle time of epidermal cells may be as short as 24 hours[11] and rapid healing will occur. As the skin (or epithelium) heals, some negative feedback must come into operation to check mitosis. It is surprising that very little research appears to have been done on these feedback mechanisms which are clearly of vital importance in regulating healthy cell growth (otherwise normal cells would continue in logarithmic growth).

The time relations of epithelial damage and repair are important in the correct timing of rest periods in the split-course treatment. Local reactions reflecting radiation damage take 2–3 weeks to develop. The response of reparative proliferation follows this and appears to be maximal between the fourth to seventh week after the beginning of each course of radiation (Fig. 2).

Table VI

LOCAL SKIN AND MUCOSAL REACTIONS TO TREATMENT (1960–1962)

Site of Primary Tumor	Cases	Degree (per cent)		
		1	2	3
Mouth, Tongue and Tonsil	15	40	53	7
Laryngopharynx (pyriform fossa and epiglottis)	25	60	20	20
Intrinsic Larynx	17	53	35	12
Postcricoid	8	50	38	12
Lung (bronchus)	33	52	45	3
Breast	14	85	15	—
Sarcoma	14	50	50	—

Definition of degrees of reaction:

(1) Transient discomfort. Erythema to dry desquamation only.

(2) Discomfort, but not interfering seriously with eating. Marked erythema. Patchy mucositis.

(3) Severe discomfort and/or dysphagia affecting rest and eating. Moist epithelitis; confluent mucositis.

The growth rate of tumor cells varies according to type and is one characteristic which determines the inherent malignancy of a tumor, but the intermitotic cycle time of tumor cells is probably seldom less than a week[4] and may often be much longer. It will also vary in different regions of the same tumor, depending on the blood supply. In hypoxic regions it will be very slow, so that the net population doubling time of the tumor as a whole will always be longer than the intermitotic period in areas of most active growth. Since radiation itself inhibits mitosis for several days or weeks after a dose of 2,000 to 3,000 rads,[9] the recovery of tumor cells will be much slower than that of normal epithelial cells under the influence of the stimulus to healing. Healing of normal tissues will be further assisted, in small areas at least, by ingrowth of intact peripheral cells and migration ("seeding") of connective tissue cells into the tumor bed. The consequence of this differential in the recovery rates of normal and malignant cells from radiation damage is vividly illustrated by a semilogarithmic graph of the theoretic kinetics of a mixed population of normal and malignant cells exposed to a typical split-course of irradiation (Fig. 2). The graph is based (for the sake of simplicity) on the assumption of fully aerobic conditions in both skin and tumor cells. This would only hold true for small, well-vascularized tumors. For larger tumors containing hypoxic and anoxic zones, sterilization of tumor cells would lag behind that of skin cells (and of other normal cells with a good blood supply also in the irradiated field). This serves to emphasize the necessity of allowing adequate time

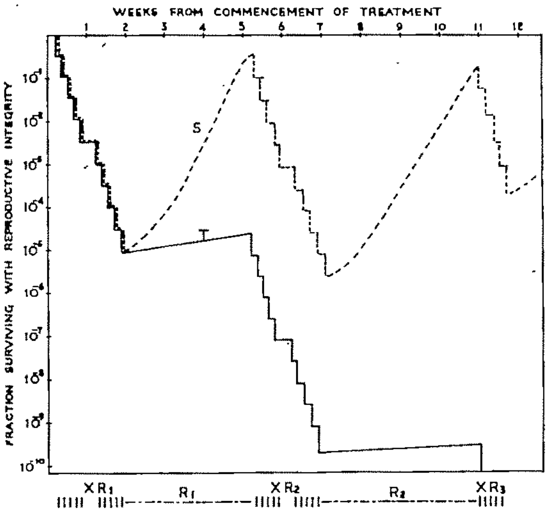

FIG. 2. Presumptive kinetics of normal (epithelial) and malignant (tumor) cells during split-course therapy. – –S– – =Squamous epithelial cells retaining integrity, showing rapid regeneration during rest periods. ——T—— =Tumor cells showing slower recovery. Population doubling time taken to be 3 weeks. XR_1=First part of radiation therapy (10 daily fractions of 275 r). R_1=First rest period. XR_2=Second part of radiation therapy (10×275 r). R_2=Second rest period. XR_3=Third course of radiation therapy (if required)—(5×275 r). (D_{37} taken=150 rads; extrapolation number=2).

for normal tissue recovery to occur if even higher tumor doses are necessary to achieve tumor destruction.

In this example, the doubling time of normal cells under the maximal stimulus to mitosis is taken as 24 hours, while the average tumor cell population doubling time is taken as 3 weeks. Very few tumors clinically doubled their mass in less than 6 weeks. To judge from length of history and the observed rate of growth of accessible tumors, such as epitheliomata of skin, oral cavity, and cancers of breast, many take several months to do so. It can be seen from the slope of the logarithmic graph that little headway is lost in terms of tumor recovery during a rest period of 4 weeks. Such a gap in the course of treatment will have no more deleterious effect than a similar period of delay in establishing the diagnosis and starting treatment. In fact, it is probably less harmful, owing to the radiation-induced arrest of mitosis. For all but very rapidly growing tumors, rest periods of from 4 to 8 weeks should be more than compensated for by an additional 500–1,000 rad tumor dose. The increased normal tissue tolerance allows much more than this to be given with safety. Although this model is speculative, it agrees reasonably well with clinical observation. Normal tissue damage, as predicted theoretically and as observed in practice, appears to need at least 3 weeks after a dose of 2,000 to 3,000 rads to recover fairly completely. Higher doses would require a longer rest period. Theory and practice thus appear to be in good agreement as regards choice of the length of rest periods. Theoretically, this process (of treating and resting) could be repeated indefinitely until no tumor cells survive. In practice, recovery of normal tissues *in vivo* as opposed to isolated cells under experimental conditions is never complete, and there must be a top limit of a safe total dose. Even so, several patients have been given 8,500 to 9,500 r skin dose (with 250 kv. roentgen rays, half value layer of 1.5 mm. Cu) by 4 part split-courses, without even a skin break and with only short periods of soreness. At the termination of treatment, the skin remained supple and was free from scarring, with only a little dryness and deep pigmentation being present. It seems reasonable to hope that, likewise, damage to connective tissues and the internal viscera may be minimized in the same way so that radiation therapy could be put to even more effective use when dealing with deep seated tumors. Although distant metastases still constitute the gravest problem in cancer treatment, we shall not succeed in eradicating many of the localized tumors, where a chance exists, unless we can deliver a much higher tumor dose without the prohibitive attendent morbidity; *e.g.*, a tumor 5 cm. in diameter (mass about 70 gm.) may contain up to 10^{10} viable tumor cells.[11] If only 1 per cent of these are seriously hypoxic, calculations indicate that the depopulation needed to give a 90 per cent chance of cure (reduction to 10^{-11} fraction) would require a single dose of 7,500 rads, or a dose of about 12,000 rads if given in 500 rad fractions. Doses of this order simply cannot be tolerated if given by continuous techniques. Present experience suggests that such very high requisite tumor doses can be approached with safety only by utilizing the split-course principle.

CONCLUSIONS

The split-course technique is by no means static or finalized. Theoretic considerations (including some not dealt with here—such as the influence of higher extrapolation number) indicate the desirability of delivering the dose in fewer larger fractions. The size of an individual fractional dose which can safely be given, especially to a large volume, is limited by the constitutional effects it produces; *i.e.*, radiation sickness, diarrhea, leukopenia, etc. It has been suggested that a new effect—"extra" damage from some other mechanism—may begin to operate on tissues *in vivo* with single doses above a certain size; *e.g.*, 1,500 r (Lajtha, unpublished). Clearly, we must proceed cautiously; but, the future trend of the evolution of radiation therapy may perhaps be towards a longer spacing of fewer, larger fractions, whatever the exact details.

Meanwhile, the split-course approach offers certain practical advantages. The family physician is less reluctant to refer patients for radiation therapy when he finds that we no longer "burn them up." Surgical colleagues are more ready to concede that radiation therapy is of real value when they note less severe reactions and tissue scarring. Irradiation does not increase the difficulties of surgery if subsequently needed, and fistulae or skin breakdown are seldom a problem in such cases, provided that operation is not deferred too long after irradiation.

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REDUCED FRACTIONATION IN RADIATION THERAPY*

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THE considerations which led us to abandon the customary daily fractionation schedule were discussed in some detail in Chapter v of the second volume of "Progress in Radiation Therapy" edited by Buschke in 1962.

The impetus for the departure from a daily treatment schedule was an emotional rather than a rational one. After gaining some experience with the cobalt 60 apparatus, the side effects of conventional roentgen therapy became of great concern to us. It was felt that not only the patients with a more favorable prognosis but all should be treated with the cobalt 60 unit, thereby subjecting them to lesser sessions and also lessening the degree of skin reaction. In order to accommodate everyone on our only cobalt 60 unit, we decreased the number of treatments and increased the single increments, spacing them in the over-all time originally planned for their course. The total dose was somewhat reduced to avoid undesirable side effects. The excellent tolerance of our first patients to this type of therapy emboldened us to extend this schedule to an increasing number of cases so that by the beginning of 1963 we had treated 317 patients as follows: 4,000 r to 6,000 r tumor dose given in 4 to 8 weeks, with about 20 treatments spaced at 48 to 72 hour intervals. We started with lower doses and increased the portions gradually to test the tolerance of the patient to the higher increments. Last year we even abandoned this slow start and now begin with the full dose unless there is specific reason for caution.

MATERIAL

Table I shows the composition of our patient material "treated for cure." Since we started late in 1957 with cancer of the lung, we cannot present any 5 year results. Because of the very heterogenous material, it is impossible to present a meaningful statistical evaluation. All patients were carefully watched for any unfavorable local or systemic side effects from the higher fractions. They appeared to tolerate this treatment far better than the patients who remained on a daily schedule. Their morale was higher and we had a comparatively low number of "drop outs"; that is, we were able to complete the planned course of treatment on practically all the patients. This is especially important in our material which consists mainly of out-patients. When treated daily, these people are prone to miss appointments because of transportation difficulties, inclement weather and minor ailments. There is no doubt that daily treatments are an almost intolerable burden, both to the patient and his family. The reduced schedule, however, occasionally saved the patients from hospitalization, helped to preserve their working ability while under treatment and diminished by two-fifths the total cost of their therapy.

Table I

TYPE OF CANCER CASES TREATED

	No. of Patients
Lung	79
Head and Neck	72
Female Genitalia	24
Central Nervous System	52
Urinary Bladder	17
Gastrointestinal	15
Breast	50
Miscellaneous	8
Total	317

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* Presented at the Forty-fifth Annual Meeting of the American Radium Society, San Francisco, California, April 1–4, 1963. Part of the Symposium: Protraction and Fractionation; Chairman, Dr. Franz Buschke, San Francisco, California.

Table II

CARCINOMA OF LARYNX (VOCAL CORD) TREATED WITH COBALT 60 TELETHERAPY

Patient	Date Treatment Began	Total Days	No. of Treatments	No. of Fields	Total Exposure Dose (rads)	Total Tumor Dose (rads)	Average Single Exposure (r)	Average Single Tumor Dose (rads)
T.M.	3/59	36	23	1	6,200	5,150	270	225
J.P.	2/60	49	26	2	7,800	5,100	300	200
S.G.	5/60	42	25	2	7,500	6,400	300	255
M.R.	9/61	47	21	1	7,000	5,000	335	240
H.E.	1/62	44	20	1	7,700	6,200	385	310
E.J.	2/62	36	18	1	6,800	5,400	380	300
J.L.	2/62	43	20	2	7,600	6,100	380	305
R.A.	2/62	50	26	2	6,600	5,600	255	215
L.S.	3/62	40	19	1	7,000	6,000	370	315
H.R.	4/62	41	20	1	6,500	5,050	325	250
M.R.	6/62	40	19	2	6,300	5,500	350	290
H.S.	5/62	57	25	2	7,250	6,250	290	250
H.L.	9/62	42	20	2	5,600	5,600	280	280
H.C.	9/62	34	20	1	6,700	6,700	335	335
C.L.	12/62	42	18	2	4,800	5,000	265	280
G.D.	1/63	45	20	1	6,000	4,300	300	215
D.S.	1/63	43	19	1	5,700	4,750	300	250
Average		43	21		6,060	5,535	320	260

For the evaluation of tumor results, we have chosen two small homogeneous groups of patients with the following disease characteristics: (1) tumors confined to a single site and easily observed; (2) tumors which produced general metastases either rarely or late in the course of the disease; and (3) tumors which at the time of treatment were under constant observation and evaluation by our surgical colleagues. These conditions are fulfilled by cancers of the vocal cord and urinary bladder.

In 18 consecutive cases of cancer of the vocal cord, there has been complete disappearance of the tumor with no side effects such as edema, prolonged hoarseness and dysphagia or any skin changes. These were patients referred to us by the laryngologist and head and neck surgeon since 1959.

Seventeen of these cases were treated 3 times weekly as out-patients. The only exception was a patient hospitalized for a nonrelated condition and treated daily. The average treatment data were a total tumor dose of 5,500 r in 43 days given in 21 sessions. Table II shows more detailed information concerning patients who were treated 3 times weekly.

The next group consists of 17 patients with carcinoma of the bladder referred to us by our urologists and followed by them with periodic cystoscopic examinations. These were far-advanced cases, unsuitable for cystectomy. Most had transurethral surgery and several had some type of partial resection by cystotomy. Twelve of the 17 cases were treated with the electron beam of the betatron unit. The initial results were favorable. It is not possible to distinguish whether the reduced fractionation schedule or the use of the electron beam was responsible for these results. The dosage schedule and results are shown in Table III.

Since the great majority of our patients with cancer of the lung manifested widespread metastases almost immediately after the completion of therapy, any attempt to evaluate the radiation effect in terms of survival would be futile. We had, however,

Table III

DOSAGE SCHEDULE IN CASES OF URINARY BLADDER CARCINOMA

Tumor Dose (rads)	Time (days)	No. of Treatments
6,000	49–56	20–24
	Initial Response	
12 cases	Excellent–disappearance of tumor	
4 cases	Good initially—tumor recurred	
1 case	Treatment discontinued—cystitis	

ample opportunity to observe that large volumes of tissue can tolerate large dose fractions.

Our present treatment schedule for carcinoma of the lung as compared to that previously used is shown in Table IV.

DISCUSSION

Radiobiologic research supports the validity of our clinical impression in an increasing number of reports.[1] Figure 1 is a graph, based upon the work of Elkind,[2] showing that fewer larger fractions enhance radiation effects.

The now customary schedule of radiation therapy 5 times weekly grew out of convenience to allow personnel a long weekend; this was not based on any scientific premises. The results were not different from those derived from the 6 times weekly schedule or even Coutard's original schedule of 11 times weekly. Our program of 48 and 72 hour intervals is more suitable biologically. Even this schedule might be too tight. Larger and wider spaced fractions must be attempted and supervoltage makes this clinically possible.

We feel strongly that with an over-all time of at least 30 days, larger fractions with greater spacing definitely show an improved tumor effect. Guided by the clinical situation, the total dose is adjusted downward. In our experience, with 3 times weekly sessions, the total dose falls about 10–15 per cent short of the dose anticipated for daily treatment. Some of our best results were achieved with doses below 5,000 rads. The patients whom we expected to do well did so and the patients whom we expected to do poorly did no worse.

Table IV

COMPARISON OF TREATMENT SCHEDULES IN CASES OF CARCINOMA OF THE LUNG

	Tumor Dose (rads)	Time (days)	No. of Treatments
Present	5,200	35–40	20 or less
Previous	6,000	55–60	35–40

SUMMARY

In summary, we feel that more widely spaced fractions have the following advantages:

1. Better tumor response.
2. Better general tolerance of the treatment by the patient.
3. Convenience to the patient through reduction of weekly visits, often enabling him to pursue his occupation and in some instances making hospitalization unnecessary.

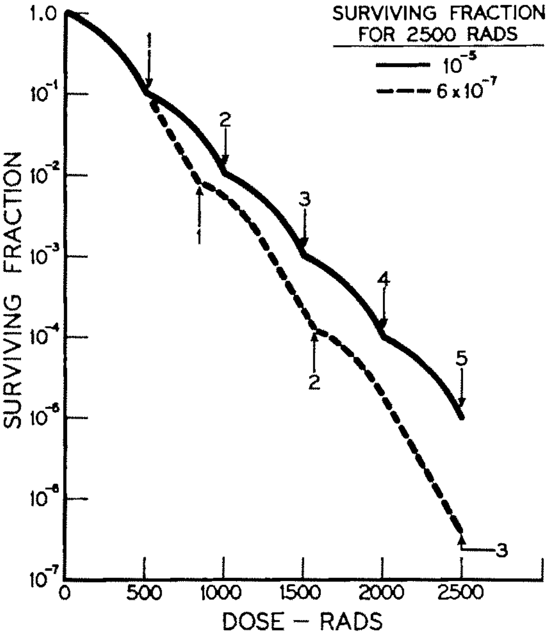

Fig. 1. Survival of Chinese hamster clone A cells irradiated to a total dose of 2,500 rads in 3 and 5 fractions. These curves are based on the work of Elkind.[2]

4. Convenience to the department by gaining free time for follow-up, treatment planning, teaching and research.

5. Economic advantage for the patients who get the total treatment in fewer sessions (or to the community which often pays the bill) as well as for the department by making it possible to treat more patients with the same equipment.

Ellis,[3] in the summary of his article about the dose-time relationship which appeared in the *British Journal of Radiology*, stated: "Hitherto, administrative convenience has been of almost more importance in radiotherapy than scientific knowledge from the point of view of deciding on treatment regimens."

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MASSIVE SINGLE DOSE, WEEKLY FRACTIONATION TECHNIQUE IN TREATMENT OF HEAD AND NECK CANCER*

PRELIMINARY REPORT

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An opportunity to assess the effects of an unconventional fractionation technique presented itself at the Columbia-Presbyterian Medical Center in conjunction with a study of the role of high-oxygen pressure in clinical radiation therapy.[17] Because of the necessity for anesthesia when a patient is subjected to 4 atmospheres of oxygen, the usual daily treatment schedule was impractical. In preparation for this oxygen study, a number of patients was treated with the same type of fractionation that had been proposed for the oxygen project but with exposure to normal atmospheric conditions, rather than breathing oxygen in a hyperbaric chamber, in order to gauge the effects on tumors and normal tissues. Preliminary results on a series of patients treated in this manner have been published.[12]

The present report is based on the analysis of two groups of patients with head and neck malignancy treated on a weekly-dosage schedule. The first group (12 patients) consists of a nonrandomized selection of patients treated to various total doses from approximately 1,000 r in a single dose to 4,000 r in 4 treatments spaced over 21 days (Table I). Most of these situations were entirely palliative in nature because of the presence of far advanced disease, often beyond the possibility of being encompassed in a reasonable radiation field.

The second group (8 patients) comprises those patients included in the oxygen project but irradiated without added oxygen (Table II). They have been randomly selected and can be compared with another randomized series of 7 patients (Table III) treated to tumor doses of 5,000 r to 6,500 r at the rate of 1,000 r/week, irradiation being given 3 times a week. The effect of high oxygen pressure will not be considered in this report.

At the present time, the series is small and the follow-up is short. Therefore, only a preliminary report can be made. Since all the patients had advanced malignant disease, it is to be expected that an extremely high percentage will die of cancer in a relatively short period of time. The only practical measure of effectiveness is the ability to control the local tumor. In most cases no attempt was made to include all the regional lymph nodes since it was felt that (a) tissue tolerance would be compromised if the treatment portals were enlarged beyond those absolutely necessary to cover the primary tumor and (b) surgery was thought better able to control lymph node metastasis in the neck. Regional lymph nodes were included only if it was not necessary to enlarge the treatment portals to any major extent.

METHOD

Patients in the randomized series were selected on the basis of having far advanced malignant disease of the head and neck region with direct extension beyond the site of origin or with regional lymph

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Table I

MASSIVE DOSE TECHNIQUE, NONRANDOMIZED SERIES

Patient	Lesion	Treatment	Tumor Control	Survival	Complications
A.K.	Moderate to poorly differentiated squamous cell epithelioma of left tonsil with postoperative recurrence in right fauces and left nasopharynx	2,000 r/7d/2 treatments to recurrence 6×8 cm., opposing fields	complete, 4 mo.	dead of persistent disease at 11 mo.	none
I.F.	Tongue with local recurrence and skin involvement after radical surgery. Squamous cell carcinoma	1,250 r×1 followed by 2,500 r/11d by conventional technique	not controlled	dead at 2 mo. with persistent disease	pain and edema after first large dose
A.S.	Post surgical recurrent squamous cell epithelioma of floor of mouth with fistula to skin	1,340 r×1	not controlled	dead at 2 mo. with persistent disease	facial edema following first large dose
C.diG.	Squamous cell epithelioma of laryngeal surface of epiglottis	2,500 r/7d/2 treatments, opposing 6 cm. circular ports	complete, 8 mo.	dead of lung primary at 8 mo.	none
N.G.	Poorly differentiated squamous cell epithelioma of tonsil and cervical lymph nodes	4,000 r/24d/4 treatments, opposing 8×10 cm. ports	complete, 7 mo. plus	dead of suicide at 10 mo.; disease status unknown	none
W.K.	Undifferentiated squamous cell epithelioma of nasopharynx, palate and nose	4,000 r/35d/4 treatments, opposing 8×10 cm. ports	not controlled	dead at 1 mo. of persistent disease	none
C.H.	Undifferentiated squamous cell epithelioma of nasopharynx with cranial nerve involvement	3,250 r/14d/3 treatments, opposing 8×8 cm. ports	partial, 5 mo.	dead at 10 mo. with recurrent disease	none
M.M.	Squamous cell epithelioma of nasopharynx, recurrent 3 yr. post radiation	2,000 r/7d/2 treatments, opposing 6×6 cm. ports	not evaluable	alive at 22 mo. with persistent disease, probable	none
G.A.	Squamous cell epithelioma of almost entire tongue and submental region	3,250 r/14d/3 treatments, 7.5×12 cm. opposing ports	complete, 22 mo.	alive at 22 mo. with bilateral cervical lymph node involvement; dead at 24 mo.	none
T.J.	Recurrent squamous cell epithelioma of larynx post surgery, with esophageal obstruction	1,083 r/1 treatment, 6×8 cm. port	not controlled	dead at 2 mo. of persistent disease	severe facial edema
J.F.	Moderately well differentiated squamous cell epithelioma of larynx recurrent post surgery to esophagus	2,500 r/7d/2 treatments, 8×10 cm. opposing ports	partial, 3½ mo.	dead at 11 mo. of persistent disease	none
T.H.	Moderately differentiated squamous cell epithelioma of tonsil, base of tongue, palate, and submandibular lymph nodes	3,250 r/14d/3 treatments, opposing 9.5×12 cm. ports	partial, 5 wk.	dead at 5 mo. of persistent disease	none

node metastasis. Lymphomas were excluded. Patients were treated according to two different regimens: (a) 3 days a week for 5 to 6 weeks or more at the rate of 1,000 r tumor dose per week; (b) on a once a week basis with the initial dose being 1,250 r to the tumor and the subsequent doses 1,000 r each for a total of 3,250 r in 14 elapsed days. All patients treated before July, 1962 are included and their status as of February 1, 1963 has been evaluated.

The remainder of the patients discussed in this report were selected mostly on the basis of having recurrent disease after prior surgery or irradiation, or widespread metastases with virtually no chance of cure. Only 3 patients in this group had a chance of permanent control of the disease. One of these patients had an epithelioma of the tonsil, base of tongue and palate, with regional lymph node involvement; another had a tumor involving almost the entire tongue and floor of the mouth and the third had a relatively small poorly differentiated epithelioma of the tonsil with involvement of an adjacent lymph node who refused the conventional type of radiation therapy. Total dose and number of fractions varied somewhat within this group as a whole.

All treatment was given on the 22.5 mev. betatron, using the roentgen-ray beam. This type of equipment is well suited to the method of massive doses because of the relatively low integral dose, homogeneous distribution of radiation, low skin dose, low bone absorption and excellent collimation. Radical neck dissection was performed where indicated, usually 4 to 8 weeks following irradiation.

TABLE II

MASSIVE DOSE TECHNIQUE, RANDOMIZED SERIES

Patient	Lesion	Treatment	Tumor Control	Survival	Complications
K.T.	Well differentiated squamous cell epithelioma of tonsil and soft palate	3,250 r/14d/3 treatments, opposing 6×8 cm. ports. Later resection	3 mo.	living and well at 26 mo., after surgical removal of disease	none
E.B.	Moderately well differentiated squamous cell epithelioma of cervical esophagus with cutaneous fistula	3,250 r/14d/3 treatments, obliqued 7.5×12 cm. ports	not controlled	dead with persistent disease at 4 mo.	none
H.H.	Squamous cell epithelioma of posterior tonsillar pillar, lateral laryngeal wall and pyriform sinus	2,250 r/7d/2 treatments (planned pleural 3,250 r/14d/3 treatments) opposing 6×10 cm. ports	2 mo.	died at 5 mo. of cerebral vascular accident during attempt at perfusion	severe mucositis
M.F.	Squamous cell epithelioma of tonsil, soft palate, floor of mouth, and gingivae; 2 positive cervical lymph nodes	3,250 r/14d/3 treatments, opposing 8 cm. circular portals. Radical neck dissection	17 mo.	living and well at 17 mo.	mucosal necrosis
A.McK.	Epithelioma of left nasopharynx with left cervical lymph node involvement	3,250 r/14d/3 treatments, opposing lateral 6×10 cm. ports. Radical neck dissection	10 mo.	died of metastases at 10 mo.	none
J.L.	Poorly differentiated squamous cell epithelioma of base of tongue, vallecula and bilateral cervical lymph node involvement	3,250 r/14d/3 treatments, opposing lateral 6×10 cm. ports. Later iridium 192 implant	not controlled	dead at 9 mo. with primary uncontrolled	none
W.T.	Moderately well differentiated squamous cell epithelioma of tonsil, retromolar trigone and base of tongue	3,250 r/14d/3 treatments, opposing 6×8 cm. ports. Radical neck dissection	8 mo.	living and well at 8 mo.	none
J.F.	Squamous cell epithelioma of antrum, palate, ethmoids and skin of face	3,050 r/14d/3 treatments, anterior 8×10 cm. and lateral 10×10 cm. ports	5½ mo.	died of brain abscess at 5½ mo.	facial edema

Table III

CONVENTIONAL TECHNIQUE, RANDOMIZED SERIES

Patient	Lesion	Treatment	Tumor Control	Survival	Complications
E.K.	Epithelioma of tonsil, pharyngeal wall, base of tongue and cervical lymph nodes	6,327 r/50d, opposing 7.5 × 12 cm. ports	not controlled	died at 3 mo. with persistent disease	none
J.L.	Undifferentiated squamous cell epithelioma of nasopharynx with bilateral cervical lymph node involvement	5,994 r/40d, opposing 12 × 15 cm. ports reduced to 6 × 8 cm. after 5,000 r	22 mo.	living at 22 mo.	laryngeal edema and hearing loss
P.R.	Chondrosarcoma of sphenoid bone	5,000 r/37d, opposing 8 cm. circular ports	7 mo., partial	dead at 9 mo. with persistent disease	none
A.A.	Undifferentiated squamous cell epithelioma of nasopharynx with unilateral cervical lymph node metastasis	6,500 r/50d, opposing 12 × 15 cm. ports reduced to 5 × 7 cm. after 5,000 r	not controlled	dead at 6 mo. of metastasis and persistent disease	none
E.O'K.	Moderate to poorly differentiated squamous cell epithelioma of base of tongue and bilateral cervical lymph node metastasis	6,400 r/48d, opposing 8 × 10 cm. ports reduced to 6 × 8 cm. after 5,000 r	not controlled	dead at 8 mo. of persistent disease	necrosis of alveolar ridge
A.R.	Moderately differentiated squamous cell epithelioma of base of tongue with unilateral cervical lymph node involvement	5,000 r/37d, opposing 9 × 15 cm. ports	2 mo., partial	dead at 5½ mo. of persistent disease	none
C.F.	Squamous cell epithelioma of hypopharynx and postcricoid region	6,000 r/52d, 3 ports 6 × 8 cm.	not controlled	dead at 3 mo. of persistent disease	none

RESULTS

Immediate tolerance to the massive doses was generally excellent. Three patients in the nonrandomized series (Table I) developed facial edema accompanied by pain or discomfort within 24 hours of the initial dose. This resulted in discontinuance of treatment in 2 patients and modification of the treatment schedule in the third. All 3 had had extensive radical surgery, including neck dissections prior to radiation therapy. Interruption of normal lymphatic drainage pathways was presumed to be an important factor responsible for the sudden onset of edema.

Skin reactions were minimal and ranged from a mild erythema to a moderate dry desquamation. No moist reactions developed despite the use of lucite bolus to increase the dose to the cervical lymph nodes. The mucosal reactions, on the other hand, were severe and in the group treated to 3,250 r in 14 days were more or less equivalent to the reactions observed with 6,000 r in 6 weeks delivered by conventional techniques. A nearly confluent membranous mucositis was usually observed at the time of the third treatment which cleared by 3 to 4 weeks following completion of therapy.

In the randomized series of the massive dose group (Table II), 1 patient (H.H.) did not receive the planned third dose of 1,000 r because of the severe mucosal reaction and had to be hospitalized for treatment of severe discomfort and dehydration. Another patient (J.F.) had the third treatment reduced to 800 r instead of the planned 1,000 r because of the severity of the mucositis.

Three patients underwent radical neck

dissections approximately 7 weeks following completion of massive dose radiation therapy without difficulty in healing although the line of resection was partly through the irradiated field. A fourth patient (K.T.) required resection of locally recurrent tumor as well as a radical neck dissection 4 months following completion of irradiation with no undue postoperative difficulty.

Tumor control appears to be more satisfactory in those patients treated with the massive dose technique when compared with the more conventionally treated group of patients. In the nonrandomized series, there are 12 patients of whom 4 had complete disappearance of all detectable tumor from 4 to 22 months. One of these had a local recurrence after 4 months. Three died, one at 8 months (of a second primary), one at 10 months (of suicide), while the third was alive at 22 months without local recurrence but with metastases and died at 24 months, presumably of metastases. Three patients had partial control, as evidenced by reduction in tumor size for 5 weeks to 5 months. Four patients had no evidence of tumor effect but 3 of these developed edema after the initial dose and the contemplated plan of therapy was not carried out. One patient could not be evaluated but was still alive 22 months after irradiation.

In the randomized series treated with the massive dose technique (Table II), 6 of 8 patients showed disappearance of tumor; two of these recurred locally at 2 and 3 months, respectively. Two patients died without local recurrence, 1 of metastases at 10 months (A. McK.) and 1 at 5½ months of a brain abscess which, in some way, may have been related to the destructive effect of the primary tumor. Two patients remain well and without evidence of disease; 1 at 9 months and the other at 17 months following irradiation, both having had radical neck dissection in addition to radiation therapy.

Only 1 patient (J.L.) in the series treated by the conventional technique (Table III) has had a sustained control of the primary lesion (and bilateral cervical lymph node metastasis). Two patients have shown evidence of partial control for 2½ and 7 months, with renewal of tumor growth after initial effect. Radiation therapy failed completely in the other 4 patients.

Late complications have not been out of the ordinary, either in frequency or severity. In the patients treated with massive doses, 1 patient (M.F.) had a mucosal necrosis of the gingiva which had essentially healed by 6 months with conservative management. The patient with the large antral tumor (J.F.) developed facial edema in the treated region. In the conventionally treated patients, 1 developed bilateral hearing loss and laryngeal edema and another had mandibular necrosis.

REPORT OF CASES

J.F. P.H. #157-43-85 (The author is grateful to Dr. Bernard Roswit, Chief of Radiation Therapy, Veterans Administration Hospital, Bronx, N. Y. for permission to report this case.) A 45 year old white male was referred for radiation therapy, having noted "soreness" of the right cheek about 8 months before, in November, 1961. Two months later swelling of the right cheek was noted. Antrotomy was performed elsewhere in April, 1962 with removal of a tumor which histologically was classified as squamous cell carcinoma, invasive, Grade II.

There was marked swelling and erythema of the right cheek with edema of the infraorbital tissues (Fig. 1). The right eye was partly closed, due to the edema. Ulceration of the skin over the antrum, secondary to tumor growth, was noted in several areas. A hard, nodular growth was present in the buccal alveolar sulcus on the right. There was no lymphadenopathy. Weakness of the left 6th cranial nerve was noted.

Roentgenograms disclosed a large soft tissue mass in the region of the right antrum, with destruction of the antral roof. Bone destruction extended posteriorly to include the ethmoid and sphenoid sinuses.

Radiation therapy was administered on the betatron at the Columbia-Presbyterian Medical Center from June 14 to June 28, 1962, through an anterior 8×10 cm. port with 2 cm. lucite bolus and a lateral 10×10 cm. port with 1 cm. bolus. A lead shield protected the right eye on the lateral port and the eye was left uncovered by bolus with the anterior port. The anterior port was given 1,250 r tumor dose on June 14 and the lateral port was used for the subsequent two treatments of 1,000 r on June 21 and 800 r on June 28. The dose was reduced from a planned 1,000 r on the last date because of a severe mucosal reaction.

At the date of the second treatment, a mild skin erythema and mucositis were present (Fig. 2, *A* and *B*). No change in tumor size was apparent. Marked mucositis and some degree of tumor regression was noted on the date of the last treatment.

Eleven days later the tumor mass had regressed so that the cheek was about normal except for a few edematous blebs where erosion had been seen before (Fig. 3, *A* and *B*), and a mild erythema. The eye could be opened to the full normal extent. Marked membranous mucositis was still present but no intraoral tumor could be seen.

At 10 weeks the mucositis had disappeared. Atrophy and early telangiectasia of the skin and edematous blebs were still present, as well as edema of the right lower lid. Depression and puckering of the skin were noted in the right infraorbital region (Fig. 4, *A* and *B*).

The patient did not keep follow-up appointments regularly, but he was seen again November 8, 1962, with ulceration of the skin of the cheek and an oral antral fistula. Marked edema was present about the right eye. The patient was admitted elsewhere in December, 1962, where he expired on December 14, 1962. Autopsy revealed the cause of death to be a large abscess involving the right temporal lobe of the brain. No gross tumor was seen but microscopic sections were not yet available at the time of this report.*

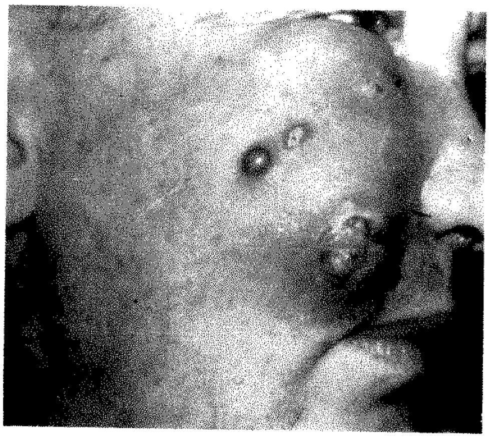

Fig. 1. Patient J.F. with right antral tumor before radiation therapy. Note marked facial swelling, edema and ulceration of skin.

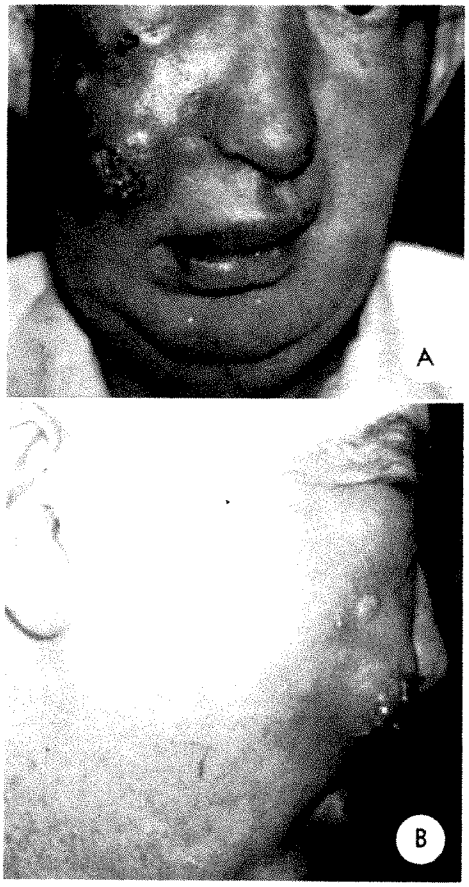

Fig. 2. (*A* and *B*) J.F., 1 week after first treatment. Essentially no change after a single dose of 1,250 r to the tumor.

W.T. P.H. #157-72-54. The patient, a 73 year old white retired bank clerk, first noted "soreness" in the right side of his throat in January, 1962. Because of continual pain, he saw a physician in April and a biopsy specimen was taken which showed a moderately well differentiated squamous cell epithelioma of the right tonsillar fossa. He was then referred to the combined Tumor Clinic of the Columbia-Presbyterian Medical Center for further evaluation and therapy.

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* This patient has subsequently died of distant metastases with the primary site free of tumor.

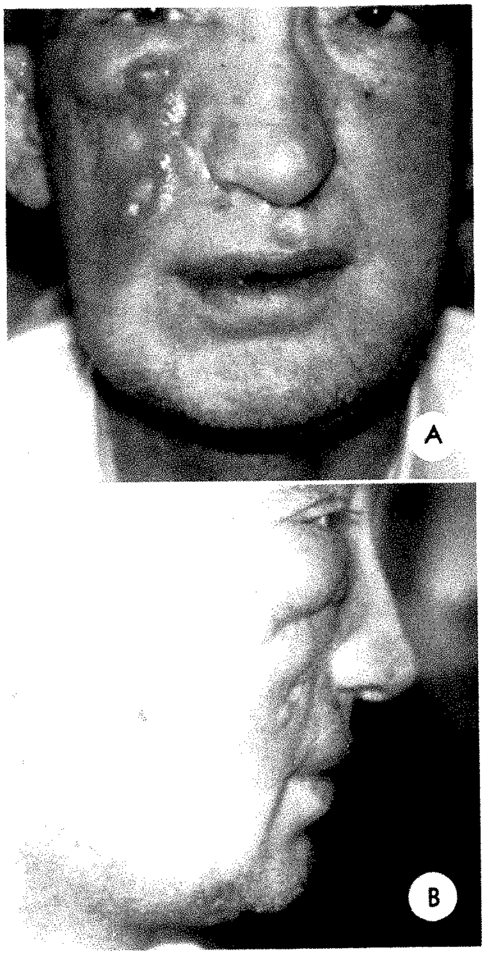

Fig. 3. (*A* and *B*) J.F., 11 days following last radiation treatment. There has been marked regression of the mass. The ulcerations of the skin are healing.

On physical examination, a large, firm, raised mass was seen arising primarily from the anterior tonsillar pillar, extending to the retromolar area anteriorly and to the pterygomandibular raphe and the base of the tongue posteriorly. A firm, 2 cm. digastric lymph node on the right, as well as several smaller posterior cervical lymph nodes were palpable.

Radiation therapy, to be followed by a radical neck dissection, was thought advisable. Radiation therapy was given on the betatron from April 19 to May 3, 1962. A total tumor dose of 3,250 r was delivered in 3 treatments, spaced 1 week apart, through opposing 6×8 cm. portals with 1 cm. lucite bolus used on the right side. By completion of therapy, the digastric lymph node had decreased to 1 cm. and radiation mucositis and epidermitis were present.

Five days following completion of therapy, the digastric lymph node and the tonsillar lesion had disappeared with only mild induration at the lateral border of the tongue in the tumor area. At 4 weeks, the radiation mucositis had disappeared.

A right radical neck dissection was performed June 26, 1962. Thirty of 53 excised lymph nodes were found to be involved by metastatic squamous cell epithelioma. No complications developed and the patient was discharged on the 12th postoperative day.

The patient has been followed in the outpatient department and remains free of clinical

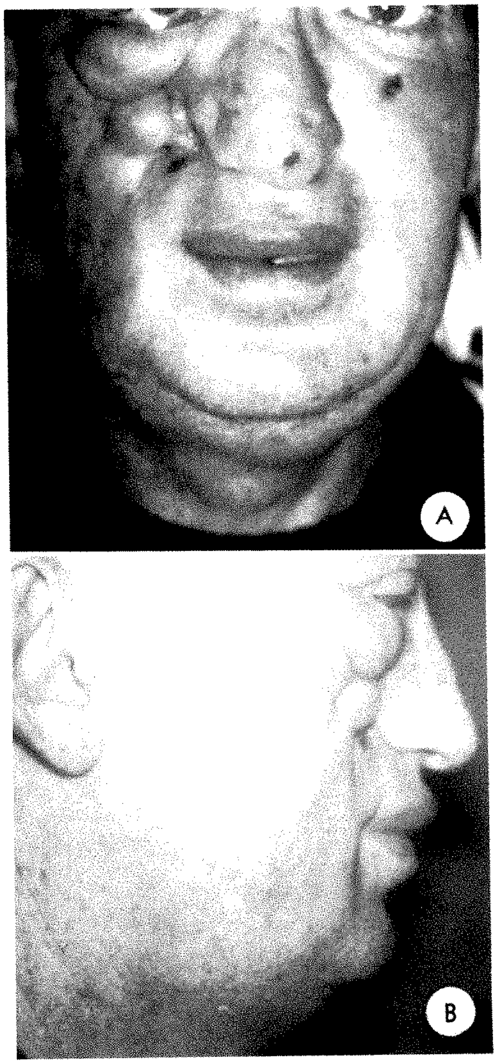

Fig. 4. (*A* and *B*) J.F., 10 weeks following radiation therapy. Edema of treated area is present. There is no evidence of tumor but puckering of skin has occurred at site of previous tumor involvement.

evidence of disease 9 months following completion of radiation therapy.*

M.F. P.H. #154-50-57. This 77 year old white man was referred for radiation therapy after having noted "soreness" of the left lower gum for 1 month. A biopsy specimen obtained elsewhere was interpreted as squamous cell carcinoma, moderately differentiated.

On physical examination, a 6 cm. exophytic, centrally ulcerated tumor was seen involving the left tonsil, both pillars and extending to include the palate, floor of the mouth, base of tongue and gingiva surrounding a 2nd molar tooth still *in situ* (Fig. 5). A 2 cm. lymph node at the level of the angle of the mandible and a 1 cm. lymph node in the mid-cervical region were noted.

Review of the biopsy specimen was reported as invasive, well differentiated squamous cell epithelioma. Roentgenograms of the mandible and chest were negative.

Radiation therapy with the betatron was given through lateral opposing 8 cm. circular ports from August 24 to September 7, 1961. One cm. of lucite bolus was used on the left port. A total tumor dose of 3,250 r was given in 3 fractions, spaced one week apart.

At completion of therapy, an intense membranous mucositis was present (Fig. 6). There was marked but incomplete regression of tumor and some decrease in size of the upper cervical lymph node. The tumor had virtually disappeared at 21 days, although some mucositis persisted (Fig. 7). Seven weeks following completion of radiation therapy, a left radical neck dissection was performed. Metastasis was found in only one lymph node adherent to the internal jugular vein. In 81 other lymph nodes excised, only chronic lymphadenitis was found. No difficulty with healing was encountered and the patient was discharged 8 days later.

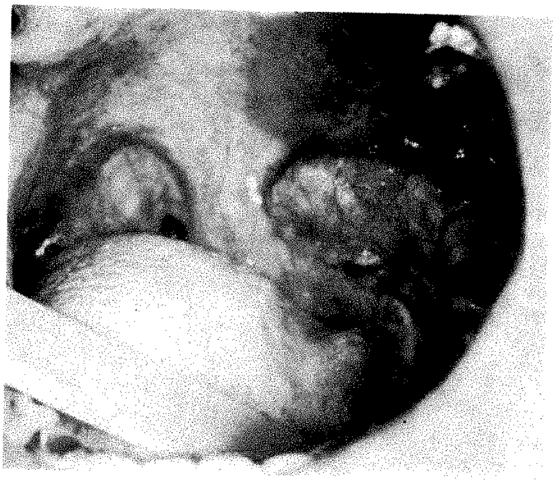

Fig. 5. M.F. before treatment. Tumor involves tonsil, soft palate, gingiva and floor of mouth.

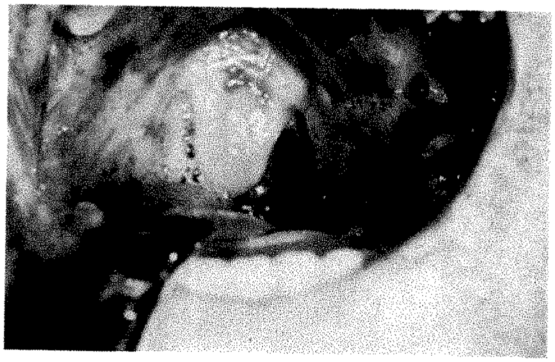

Fig. 6. M.F. at date of last treatment. Marked regression of tumor is apparent as well as the presence of a marked membranous mucositis.

Six weeks following the neck dissection, an area of mucosal necrosis 1 cm. in diameter was noted on the lingual surface of the mandible at the region of the angle with visible bone noted in this region. Under conservative management, this area virtually healed in 6 months. No evidence of necrosis or tumor recurrence was noted in February, 1963, 17 months after completion of radiation therapy (Fig. 8).

DISCUSSION

A basic factor to be considered in a discussion of fractionation in radiation therapy is the rate of recovery of cells, both in normal tissues and in tumors, following an exposure to radiation. The recovery of mitotic ability or reproductive integrity of cells in tissue culture has been amply demonstrated.[6,7,8] The study of this effect has been extended to *in vivo* systems.[2,3,11] The "shoulder" of the type C survival curve, when the extrapolation number is greater than 1, indicates a decreasing efficiency of irradiation when administered with increasing fractionation.[1] When the

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* Subsequent report states that no microscopic evidence of malignancy was found although complete examination of the antrum was precluded by extreme friability of the bone structures.

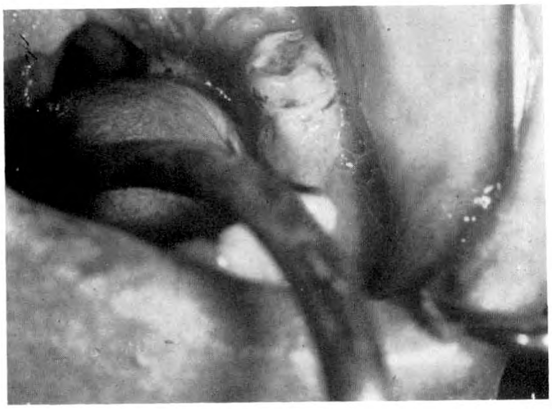

FIG. 7. M.F., 3 weeks following completion of radiation therapy. Mucositis is still present. The tumor has virtually disappeared.

extrapolation number is 1, no recovery is indicated and the surviving fraction after a given dose of radiation is the same whether the dose is given in one or more than one increment. This situation holds true for high LET radiation[3] and questionably in an anoxic environment.[8]

Models have been devised to indicate what order of radiation dose is required to sterilize tumors of various sizes.[7,14,15,18] It is clear that lower total doses are required when fewer fractions are given, provided the doses are spaced less than one generation-time apart. These analyses consider only the direct cellular effects of radiation. Indirect effects, host factors and normal tissue reactions are also important but difficult to evaluate.

The concept of therapeutic ratio involves recovery factors in normal tissues as well as in tumor cells. These have been thoroughly discussed by DuSault[4,5] on the basis of work performed by herself and other investigators. Those normal tissues which receive radiation doses as high or higher then the tumor cells are limiting factors in radiation therapy. As higher energy beams have become available for clinical work, the normal tissue reactions which must be considered limiting factors have changed. Formerly, because of lower penetrability of the beam generated by 200–250 kv. peak equipment, the skin frequently received a radiation dose as high or higher than the deeply situated tumors. Because of increased absorption in bone, necrosis is a hazard more likely to be encountered with these orthovoltage radiations. Even with supervoltage radiations in the 1–3 mev. range, certain structures, such as the spinal cord and subcutaneous tissues may receive higher doses than the tumor tissue.

Systemic effects partly due to scattered radiation can limit the size of a single dose of radiation. With high energy beams, side scatter and integral dose have been reduced and larger single doses have been better tolerated. In a study such as this, the roentgen-ray beam of the betatron at 22.5 mev. is ideal. There is essentially no side scatter, bone absorption is at close to the minimum (except for that due to pair production) and the highest dose in tissue is almost always at the tumor site. Homogeneity is excellent. These factors have an important bearing on the expected incidence of complications.

With the stimulus provided by knowledge gained from recent biologic studies and the availability of improved equipment, it seems reasonable to re-examine the question of optimum fractionation for radiation therapy of human malignancy. Many variations are possible and in this study the interval between treatments was selected on an empirical basis dictated by practical requirements. It may be probable that some other form of treatment fractionation schedule will be better or that the optimum

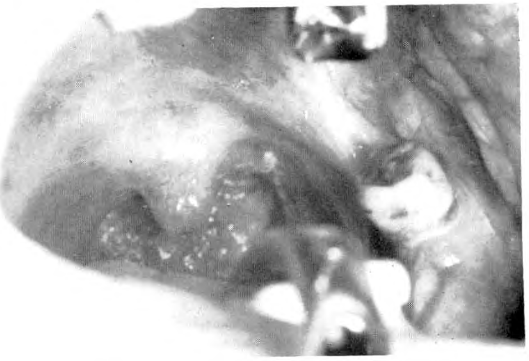

FIG. 8. M.F., 17 months after radiation therapy. No tumor can be seen.

schedule may differ for various histologic types or individual tumors. Some attempts have been made to define this optimum schedule,[9,10,13] but no practical method is available at the present time.

The dosage schedule which has been selected is the result of the observation of a large number of patients treated to various total doses. It is believed that the dose of 3,250 r in 14 days given in 3 fractions is biologically equivalent to doses in the range of 6,000 r in 6 weeks given with daily fractionation, so far as the immediate mucosal reactions are concerned. In a study by Sambrook *et al.*,[16] where various treatment schedules were used, the superiority of twice a week fractionation to daily treatment at least for breast carcinoma was demonstrated. Necrosis developed with once a week fractionation but the same total dose of 4,000 r in 4 weeks was given as in the more frequent fractionation schedule. It is possible that as good a cure rate with less necrosis might have been obtained with a lower total dose.

One might expect a higher incidence of complications with this once a week schedule, which is contrary to the treatment methods in general use based on years of clinical experience. This would be acceptable if the severity and number of complications are not too great and if the cure rate can also be increased. In this series, complications have not been excessive; in fact, they have been surprisingly low to date. It is preferable to keep the treatment fields as small as possible and to avoid the spinal cord. The central nervous system and intestinal tract are very sensitive to these massive doses. After extensive radical surgery, the method is to be avoided, even with small fields, because of edema secondary to inadequate lymphatic pathways. The results, so far, are preliminary because of the small number of patients and heterogeneity of the material, as well as the short follow-up period. What has been demonstrated is that these large doses are immediately well tolerated, that complications seem to be at an acceptable level, and what appears to be long term control of advanced primary lesions has been achieved in several instances. Extreme caution, however, must be observed in interpreting these very early results.

Should this method prove superior or even equal to presently accepted modes of fractionation it offers some very definite advantages. It requires less traveling for patients who live at some distance from the radiation facilities and the necessity for hospitalization is diminished. More time is available to treat more patients on supervoltage equipment. It is more economical, so far as cost of treatment, travel expenses and hospitalization are concerned. In palliative situations, less of the patient's remaining life-time and resources are involved in radiation therapy.

CONCLUSIONS

1. A series of patients treated on a once a week irradiation schedule with supervoltage equipment has been presented.
2. The feasibility of this treatment schedule has been demonstrated. Complications have been at an acceptable level and short term results indicate a favorable response.
3. Several advantages of the method have been considered.
4. Further study is necessary before this method can be accepted on more than an experimental basis.

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CONCLUSION OF THE SYMPOSIUM ON PROTRACTION AND FRACTIONATION*

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As I suggested in the Introduction, certain *clinically* useful tentative conclusions appear possible.

First, there appears to be little doubt that sufficient prolongation of the over-all treatment time is the most important factor from the point of view of preservation of normal tissues, particularly of vasculo-connective structures. From our own experience, initiated and supported by Baclesse's earlier analyses, it would seem that, from this point of view, the critical time is around 6 weeks. It appears that by prolonging the over-all treatment time to more than 6 weeks we can avoid almost all undesirable damage to the vasculo-connective tissue and in this way eliminate most of the late sequelae of radiation therapy. I have documented this from our own experience elsewhere.

Second, it becomes increasingly certain that such prolonged treatment does not significantly alter the possibility of controlling the tumor, at least as far as epidermoid carcinoma is concerned. This, then, would mean that the prolongation of over-all treatment time is one of the most important factors for increasing the differential between effect on the tumor and effect on the vasculo-connective tissue. The awareness of this situation and its increasingly common utilization, it seems to me, are probably the greatest progress radiation therapy has made during the last decade.

Third, in comparison to the importance of the over-all duration of therapy, details of fractionation during such protracted periods of over-all time appear to be of less importance, and can therefore be subordinated and in part adjusted to practical and economic considerations without jeopardizing the results. It seems that we are permitted to draw this very tentative conclusion and proceed with further investigations based on this conclusion.

I should like to add one remark with regard to the split-course technique: observations in a number of instances have supplied us with some marginal, and not initially intended, interesting advantages. We have seen regressions of tumor after the first part of the split course which had not been expected at this dose level (around 3,000 r). This seems to be important from the point of evaluating the synergistic effect of radiation therapy and chemotherapy which has become so fashionable in recent times.

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* Presented at the Forty-fifth Annual Meeting of the American Radium Society, San Francisco, California, April 1–4, 1963.

RESULTS OF ULTRAFRACTIONATION RADIATION THERAPY IN BREAST CARCINOMA*

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BEGINNING in 1952, postoperative radiation therapy of carcinoma of the breast was modified at the University of Chicago Clinics to a technique employing the principles of ultrafractionation. Baclesse[1] and Lenz[10] had reported their experiences with this approach. A preliminary study was presented by one of us[11,12] in 1955. In 1956, this ultrafractionated approach was adopted at Columbus Hospital, and this group is included in this study to answer the question of applicability of such a technique in general practice.

METHODS AND MATERIALS

Between January 1, 1952, and December 31, 1959, there were 168 female patients referred for postoperative radiation therapy of whom 131 patients were from The University of Chicago Clinics and 37 from Columbus Hospital. All patients had had a radical mastectomy, none gave evidence of distant metastasis and all were in apparent good health. Included in the results as failures are all patients: who did not finish therapy because of medical complications such as hepatitis (8); who died during therapy (5); who refused further treatment (3); who died of intercurrent disease (8); and who were lost to follow-up (2).

The radical mastectomies were performed by various surgeons, including residents in training. No standardized criteria of operability (such as those of Haagensen and Stout[6,7]) were followed.

STAGING AND SELECTION OF CASES

The staging is based on a mixed classification utilizing both clinical (Portmann) and pathologic data and is as follows:

Stage I—Localized lesion without skin involvement or fixation; no movable lymph nodes
Stage II—Movable localized lesion in breast with skin not involved or only slightly edematous or ulcerated over tumor, tumor cells in axillary lymph nodes
Stage III—Tumor diffusely infiltrating breast with fixation of tumor to chest wall or breast, or edema of breast or secondary tumor nodules; axillary lymph nodes may be fixed; no evidence of distant metastases
Stage IV—Tumor and skin as above, but supraclavicular lymph nodes involved or distant metastases

As the surgeons referred largely patients with histologic evidence of lymph node invasion, there is a predominance of Stage II cases. Cases were distributed as shown in Table I: Stage I, 34; Stage II, 121; Stage III, 7; Stage IV, 2. All had evidence of supraclavicular metastases. The patients' ages ranged from 20 years to 80 years with the majority being between 40 to 50 years, as shown in Table II.

Table I

STAGE DISTRIBUTION

	Total	University of Chicago Clinics	Columbus Hospital
Unclassified	4	4	0
Stage I	34	14	20
Stage II	121	107	14
Stage III	7	4	3
Stage IV	2	2	0

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* From the Department of Radiology, The University of Chicago, and the Argonne Cancer Research Hospital, and The Columbus Hospital.

Presented at the Forty-fifth Annual Meeting of the American Radium Society, San Francisco, California, April 1–4, 1963.

Table II

AGE DISTRIBUTION

Decade	Total	University of Chicago Clinics	Columbus Hospital
20–29	2	1	1
30–39	32	23	9
40–49	53	42	11
50–59	45	39	6
60–69	26	20	6
70+	10	6	4

TREATMENT TECHNIQUE

Treatment was started about 10 to 14 days after surgery and was given to the adjacent lymph nodes, *i.e.*, the internal mammary, axillary, supraclavicular and infraclavicular, and the inferior cervical lymph nodes as well as the chest wall. Five portals were used as shown in Figure 1: (1) a single anterior sternal field including both internal mammary chains and all intercostal spaces; (2) a field, without bolus material, with radiation applied tangentially from the medial and lateral sides of the patient, arranged to encompass the chest wall, extending laterally from the mid-axillary line, medially to the adjacent lateral margins of the internal mammary chain, superiorly to the inferior margin of the shoulder portal (described below), and inferiorly to the lower extent of the incision. The treatment set-up for the lateral tangential port is shown in Figure 2; (3) anterior and posterior fields, also without bolus, cross-firing and encompassing the supraclavicular and infraclavicular, axillary and lower cervical areas. The arm was elevated and extended so that the supraclavicular and axillary areas were on the same plane, as shown in Figures 3 and 4.

The planned tumor dose was 6,000 rads throughout the thickness of the chest wall, to the lymphatic tissue of the shoulder area and the base of the neck, and 4,500 rads to the internal mammary lymph nodes. This dose was delivered with daily increments, 5 or 6 per week, in an over-all period of 11 to 14 weeks.

The technical factors at the University of Chicago were 250 kv. focus skin distance 50 cm., half value layer 1.5 mm. Cu to the chest wall, half value layer 3.0 mm. Cu to the other two fields. At Columbus Hospital telecobalt was used at a source skin distance of 80 cm., treating the anterior shoulder field, the posterior field being omitted. Initially, telecobalt was also used for treating the sternal field at a source skin distance of 56 cm., but because of the fre-

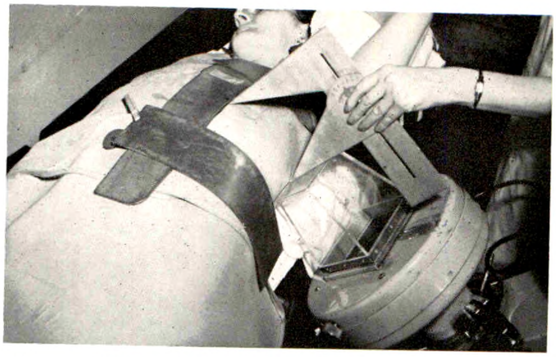

Fig. 2. Photograph showing the treatment set-up of the lateral tangential chest wall.

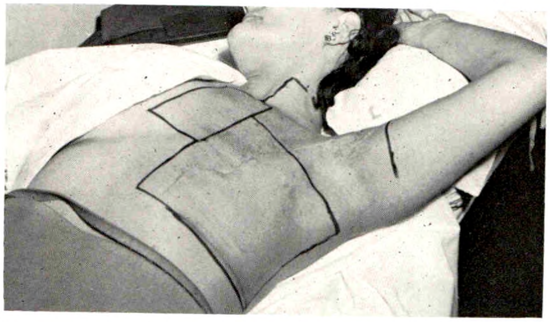

Fig. 1. Photograph showing the portal areas of the sternum, chest wall and anterior supraclavicular region.

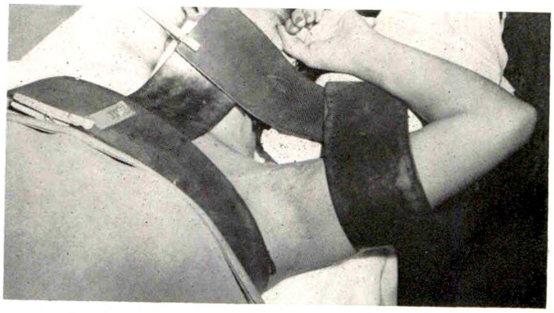

Fig. 3. Photograph showing the treatment portal of the anterior supraclavicular area.

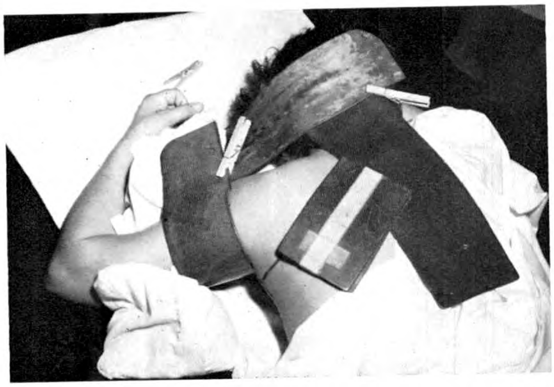

FIG. 4. Photograph showing the treatment portal of the posterior supraclavicular area.

quency of troublesome esophageal and tracheal symptoms and the occurrence of 2 cutaneous recurrences, this was discontinued and conventional roentgen therapy was resumed. Prophylactic castration by irradiation or surgery was performed on 117 patients who were either still menstruating or within 5 years of the menopause.

COMPLICATIONS

Immediate morbidity with this technique was seen in 17 patients. Ten patients experienced a severe dry epidermitis, 6 a wet epidermitis and lymphangitis occurred in 1. Another complication noted during the latter part of the treatment course, often 6 to 8 weeks after completion of the therapy, was a mild to severe radiation pneumonitis in 13 patients. This responded readily to antibiotic or expectant therapy. There was no permanent disability. Early in the series, treatment was given to the supraclavicular portals with the arm at the side and with bolus; however, after revision of the field with extension and elevation of the arm and removal of bolus from these areas so that less lung tissue was included in the irradiated block, the incidence and severity of this complication decreased. Routine chest roentgenograms following therapy showed a minimal to a moderate degree of apical fibrosis.

In 4 cases nonmalignant ulcers occurred in the irradiated breast portal. One required surgery and grafting; another healed slowly with conservative management. The remaining 2 cases are of recent onset.

RESULTS

Survival curves derived by the actuarial method of Berkson and Gage[2] show 70.1 per cent 3 year survivals, 54.3 per cent 5 year survivals and 41.6 per cent 10 year over-all survivals (Fig. 5). Little difference was noted between the survival curves of The University of Chicago patients and those at Columbus Hospital; therefore, both groups are considered together. At the time of the last follow-up, 70 patients were symptom free, 2 were ill without neoplasm, 10 were ill with neoplasm, and 7 were alive but their condition was unknown.

The second facet of the study was the evaluation of local recurrence. Only 8 patients developed histologically proven recurrences in a treated area, 7 on the chest wall (4.1 per cent), 2 in the supraclavicular fossa (1.2 per cent) and 1 in the axilla (0.6 per cent). These patients were treated by surgery and/or chemotherapy rather than by further radiation therapy. Two of the 8 are still alive with disease.

DISCUSSION

Untreated breast cancer patients have an 18 per cent 5 year survival rate from the onset of symptoms, as reported recently by Bloom *et al.*[3] confirming Daland[4] and Greenwood's statistics. About 3.8 per cent

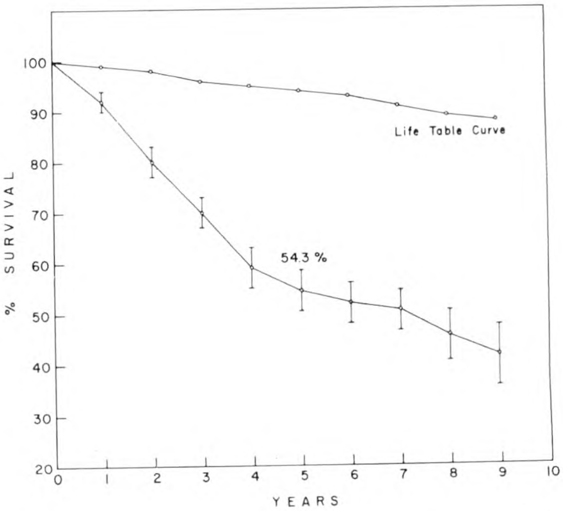

FIG. 5. Survival curve with standard deviation of the patients treated by postoperative ultrafractionated radiation therapy.

of these survive 10 years without treatment. Using these results as a base line, it is a challenge to the clinician to increase survival.

Halstead and Willy Meyer introduced the radical mastectomy in 1886 and reported a 28 per cent 5 year survival. Subsequently, further improvements have been reported with these operative approaches which currently can be divided into 4 primary attacks: (1) radical mastectomy with *en bloc* dissection of breast tissue and axillary lymph nodes; (2) radical mastectomy with dissection extended into the internal mammary and supraclavicular areas; (3) simple mastectomy with radical radiation therapy; and (4) radical mastectomy and postoperative radiation therapy.

The over-all survival rate, as reported by Haagensen and Stout,[7] using their criteria of operability and radical mastectomy is 47.2 per cent; Urban[15] with selection and an extended radical mastectomy reports 66 per cent; using simple mastectomy, as recently reported by Kennedy and Miller,[9] resulted in an over-all 5 year survival rate of 45 per cent; McWhirter[13] with simple mastectomy and radiation therapy had a 42 per cent 5 year survival for his entire group, and 58 per cent for the operable cases; while DeMoor *et al.*[5] and others using radical mastectomy and postoperative radiation therapy report a 45.5 per cent survival rate. Our over-all 5 year survival rate is 54.3 per cent (Table III).

Table III

RESULTS OF TREATMENT IN OPERABLE PATIENTS

	No. of Patients	5 Year Survival (per cent)
Kennedy and Miller[9]	212	45
Urban[15]	200	66
McWhirter[13]	1,063	58
DeMoor *et al.*[5]	313	45.5
Kaae and Johansen[8]		
McWhirter Method	187	67
Extended Method	159	69
Present Series	168	54.3

Of note is the control study by Kaae and Johansen[8] of extended radical mastectomy versus the McWhirter method of treatment, which demonstrated no significant difference in over-all survival between Stage I (67 per cent) and Stage II (69 per cent) patients.

A comparison of the incidence of local recurrence after radical mastectomy and after various irradiation or surgical approaches is of interest. With the standard Halstead procedure, the skin flaps may be the site of cutaneous recurrence with an incidence reported as high as 45 per cent in the series of Peterson and Krippaehne[14]; if skin grafts were used, the incidence was reduced to 28 per cent in their hands. Other authors report between 12 per cent and 23 per cent recurrences with various approaches. Kaae and Johansen[8] noted a 10 per cent recurrence on the chest wall and 13 per cent in the axillary region with radical surgery alone. DeMoor *et al.*[5] report 22 cases of 165, or 13 per cent, and 13 cases of 68, or 19 per cent, with chest wall recurrences when this area is not irradiated. With adjuvant radiation therapy, this was reduced to 5 per cent. Our series shows 4.2 per cent chest wall recurrences and compares favorably with that of DeMoor *et al.*[5] (Table IV).

SUMMARY

1. A group of 168 patients drawn from private practice and from a University practice was given radiation therapy by an ultrafractionation technique following radical mastectomy where residual regional disease was suspected or proven.

2. The over-all survival rate at 5 years was 54.3 per cent.

3. Cutaneous recurrence on the chest wall was noted in 4.2 per cent and regional lymph node recurrence in 1.7 per cent of the patients. These figures are more favorable than those reported when surgery alone was used and comparable to the results obtained with short courses of radical radiation therapy.

4. Morbidity was appreciably less and patient comfort considerably greater than reported in patients given short courses of radical radiation therapy.

TABLE IV

INCIDENCE OF CHEST WALL AND REGIONAL LYMPH NODE RECURRENCE

		Chest Wall (per cent)		Regional Lymph Nodes (per cent)	
Kaae and Johansen[8]	McWhirter Method		7		8
	Extended Method		10		13
DeMoor *et al.*[5]	Surgery Alone (165 Patients)	(22)	13	(7)	4
	Peripheral Field and Chest Wall Irradiation	(11)	5	(6)	3
	Peripheral Field Irradiation Only (68 patients)	(13)	19	(3)	4
Present Series	(168 Patients)	(7)	4.2	(3)	1.7

CONCLUSION

Ultrafractionated radiation therapy to the postoperative breast carcinoma patient adequately controls the disease in the operative site as well as in the regional lymph nodes, but does not modify the problem of dissemination of distant metastases. The immediate morbidity is less with this type of treatment than with short intensive courses of irradiation. On the basis of these findings, we feel that postoperative radiation therapy is a worthwhile procedure.

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We wish to acknowledge the assistance of Mrs. Ethel Rosenberg and Paul Meier, Ph.D. for their aid in the statistical analysis.

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DESCRIPTION OF A METHOD AND RESULTS OF TREATMENT OF BREAST CARCINOMA WITH COBALT 60 TELETHERAPY*

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IN THIS paper a method of treating breast carcinoma by a radiation technique which is a modification of that used by McWhirter[18,19] is described. Methods of radiation therapy vary with the philosophy of treatment. One method is to treat only the clavicular-axillary and internal mammary lymph nodes. In some institutions no postoperative therapy is administered. In others, tissue doses of 2,000 r to 6,000 r may be given in 2 to 10 weeks. Many irradiate postoperatively only when the axilla has been involved. Since the avenues of cancer spread from the breast are multiple and unpredictable, we feel that all possible local pathways should be irradiated. Our method is to treat the lower cervical chain of lymph nodes, the clavicular-axillary and internal mammary lymph nodes, and the chest wall as a unit.

One finds a variation in the incidence of skin recurrences ranging from 15 to 41 per cent,[4,20,21] depending on the stage of disease and the surgical procedure. Local direct spread to the pleura occurs especially with fascia fixed masses. Urban,[25] and Handley and Thackray[9] have shown the frequency of metastatic disease in the internal mammary chain to be 12 to 48 per cent. When the axilla is positive, these lymph nodes are involved in 48 per cent of cases and, when the axilla is negative, in 10 to 15 per cent of cases. Wangensteen[28] and Andreassen *et al.*[1] have shown that the supraclavicular lymph nodes are involved in 33 per cent of the cases where the axilla has positive lymph nodes. Involvement of the cervical lymph nodes is only an extension of spread from the clavicular sites through connecting channels. There is no way of knowing how frequently cancer cells spread through the intercostal pathways to the spine, skull or pleura, or how often there is blood borne dissemination. There is no test to indicate whether one is dealing with local disease or generalized carcinoma even when the roentgenographic findings are negative and there are no evident metastases.

One must therefore treat those sites most frequently involved, hoping that the disease process is still localized. In radiation therapy the aim is to sterilize or contain metastatic sites without producing any significant complication in the adjacent normal tissues. To do this, an effective tumor dose is necessary in a specific treatment time.

An analysis of 112 cases treated and followed from April, 1957 to May 1, 1962 is made as to stage, survival time, incidence and initial roentgenographic appearance of pulmonary changes and their clinical course, effects on lymph nodes, skin nodules and arm edema. The frequency of skin metastases and lung metastases is reported.

METHOD

The method of treatment consists of irradiating the supraclavicular and axillary lymph node areas through two opposing ports, and the internal mammary lymph chains with the chest wall including the scar area through two tangential ports.

The anterior clavicular-axillary port extends from 5 cm. past the midline on the contralateral side to a line on the upper arm just past the axilla of the ipsilateral side. The upper margin of this field extends

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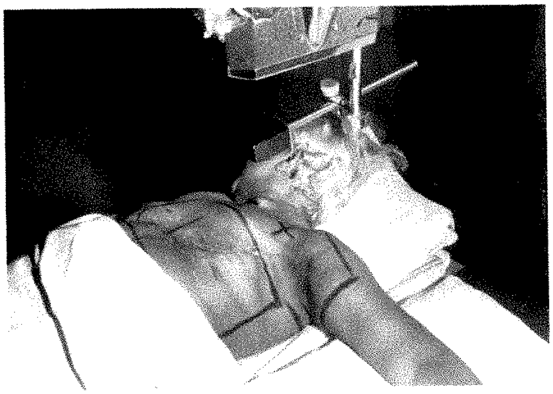

Fig. 1. Set-up for anterior supraclavicular-axillary port.

from the mid-cervical lymph node area along the superior part of the shoulder to the upper arm outside the axilla. The lower margin goes across the chest wall and includes the axillary region. When outlining and treating this field, the arm of the patient is extended at right angles to the body. The size of the field may vary from 9 by 20 cm. to about 11 by 25 cm., according to the size of the patient. The set-up of the patient is shown in Figure 1. The larynx is protected by a lead block. In order to have uniform irradiation, the axillary area is bolused with rice bags as shown in Figure 2. If there are any skin nodules, a layer of bolus about 1 cm. thick is used to cover these; otherwise, the skin nodule near the surface may receive only about one-third of the maximum dose.

The posterior supraclavicular-axillary port starts on the ipsilateral side of the spinal cord and then covers the same region as the anterior port (Fig. 3). Here, too, the axillary area is filled with rice bolus bags.

The lateral mark for the tangential fields is made so as to include all the lower axillary lymph nodes. This generally extends from the posterior axillary fold to the plane which goes through the bottom of the scar line, a distance of about 15 cm. in the average patient and 20 cm. in a large patient.

In order to find the line of entry for the medial tangential port, a chest contour through the midplane of the tangential fields is made. This generally cuts the patient through the nipple of the contralateral breast. Two thicknesses of Johnson and Johnson 3 inch wide Zoroc resin plaster bandage folded in half are used. In order to have certain reference marks on the patient and on the contour, a midline is drawn over the sternum from the manubrial notch to the xiphoid process. The intersection of this line with the contour and the intersection of the lateral line with the contour are marked on the contour. The resin plaster hardens in about 5 minutes. It is then cut on both lateral sides, removed from the patient, and the cut edges are plastered together and allowed to dry. Figure 4 shows the contour being cut on the patient before removal. The plaster bandage contour is outlined on tracing paper and the central and the lateral reference

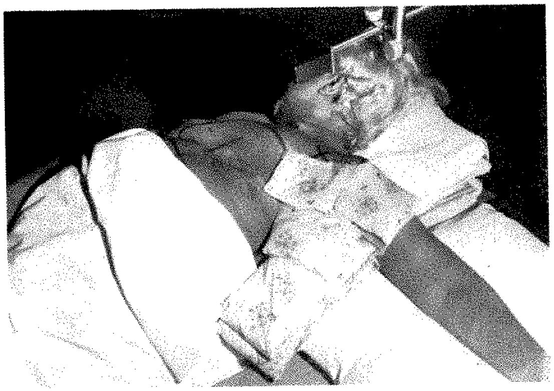

Fig. 2. Set-up for anterior supraclavicular-axillary port using rice bolus bags.

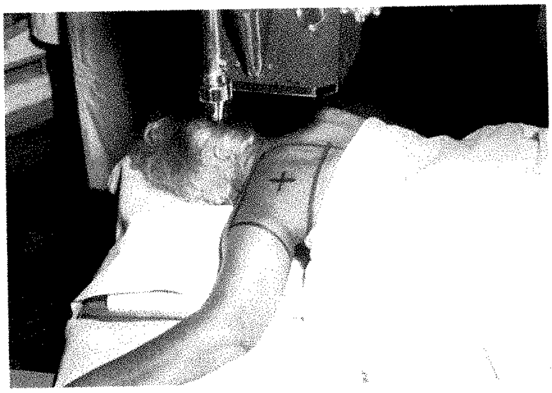

Fig. 3. Set-up for posterior supraclavicular-axillary port.

marks are designated. The anatomic limits of the internal mammary lymph nodes are drawn on the tracing paper, 5 cm. lateral[8] from the sternal center and 2 cm. deep. A line is then drawn from the lateral skin mark through the contralateral internal mammary lymph node and extended to the contour outline; this shows the edge of the tangential fields. The intersection with the contour outline marks the point of entry of the medial tangential field. The distance of this point from the central mark, which generally ranges from 7 cm. to 9 cm., is measured and is transferred to the patient by marking off this distance with a tape measure from the midline previously indicated on the patient's skin. Through this point a line perpendicular to the midplane of the patient is drawn. This then is the line of entrance and exit of the two opposing tangential fields. Figure 5 shows the contour on tracing paper; Figure 6 shows the tangential fields outlined on a patient.

The treatment set-up through the medial tangential field is shown in Figure 6. The treatment cone is placed on the medial line and the back plaque, after its crosslines have been lined up with those of the cone field, is placed on the lateral line so that the edge of each barely touches a plane through the bottom of the supraclavicular-axillary port. The light device is used to help in this set-up. The patient stretcher is rotated so that the upper edge of the light field is contiguous with the lower outline of the supraclavicular-axillary port.

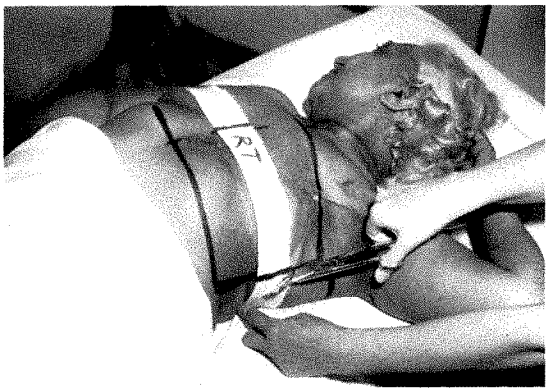

Fig. 4. The plaster contour is cut on both lateral sides before being removed.

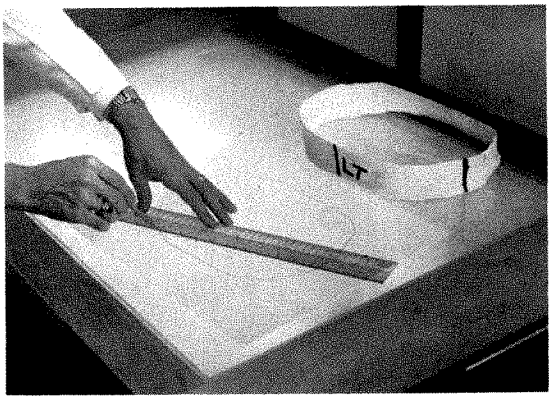

Fig. 5. Contour is traced on tracing paper, showing the internal mammary lymph nodes, the edge of the tangential fields and the point of entry and exit of the radiation.

In most cases a 10 by 15 cm. plastic cone is used with a back plaque, the area of which is covered by a 10 by 15 cm. field at 27 cm. from the cone, for our source skin distance of 80 cm. Twenty-seven centimeters is the average transverse distance between the two opposing tangential fields. The size of this plaque is determined by the ratio of the source skin distance and the source skin distance +27 cm. The outline of the field is given by the light device. For our apparatus the 30 per cent isodose line, as found experimentally, is along the light outline, and at 0.5 cm. within the light field the isodose value is 50 per cent. Since the supraclavicular and tangential light fields are made contiguous, the area between the

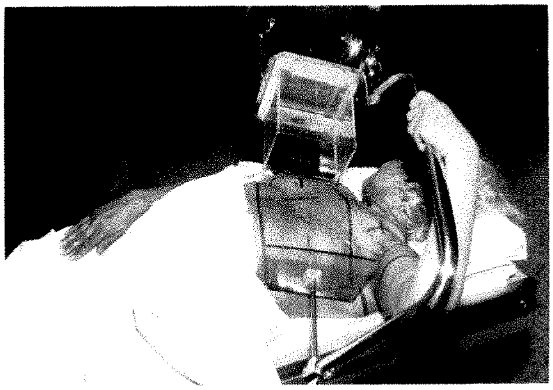

Fig. 6. Set-up for medial tangential field.

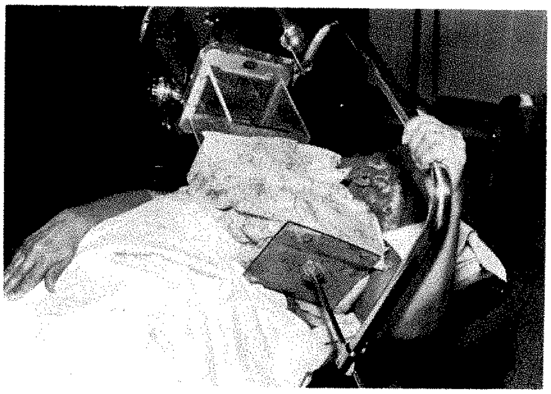

FIG. 7. Set-up for medial tangential field using a bolus.

two fields may overlap a few millimeters; in this case the dosage would be between 60 and 100 per cent of the central dose. In our experience an increased reaction along the contiguous outlines of these ports has not been noted. Because of the uncertainty of this region we try not to have the line of contiguity drawn across known disease. Once the method of setting up for a particular cobalt unit is understood, the positioning of patients becomes a simple matter.

After the patient is positioned for the medial tangential field, the back plaque is locked in place and rice bolus bags are used to fill in the space between the cone and the back plaque. Our bolus bags, 26 cm. ×12 cm., are made of washable plastic. The set-up with bolus is shown in Figure 7.

In setting up for the lateral tangential field, the entering port is now at the lateral aspect of the patient and the exit port along the medial line. We turn our patient's stretcher around and then angle the radiation beam upward toward the same wall as for the medial port. The treatment cone is placed on the lateral line, with the back plaque on the medial line and the edge of the upper light field along the bottom outline of the supraclavicular-axillary port. Here, too, the patient's stretcher is rotated so that the long axis of the stretcher is slightly off the perpendicular to the plane of radiation beam. In setting up the back plaque, the crosslines through its center are matched to the crosslines of the field. Once the patient has been set up, the back plaque can be rotated to serve as a holder for the bolus, which here, as for the previous tangential field, should fill the space between the cone and the back plaque.

DOSAGE CALCULATION

We deliver a daily dose of 200 r to the midplane of the two supraclavicular-axillary ports and to the midplane of the two tangential breast ports. Each port is

TABLE I

3,000 C-Co^{60} UNIT, OPPOSING PORT THERAPY TREATMENT TIME AND "SKIN" DOSAGE CHART FOR 80 CM. SOURCE SKIN DISTANCE

Time in minutes to treat each port in order to give 100 r tumor dose from two opposing ports and "skin" dose, max. r, including exit for 100 r at midplane for period Oct. 1, 1960 to Dec. 31, 1960
Output 23.0 r/min. at 80 cm. S.S.D.

Thickness in cm.	Area in Sq. Cm.					
	100		200		400	
	Max. r	Min.	Max. r	Min.	Max. r	Min.
10	99	2.73	99	2.68	99	2.64
11	100	2.84	100	2.77	100	2.70
12	101	2.93	100	2.85	100	2.78
13	102	3.03	101	2.94	101	2.87
14	104	3.14	102	3.03	102	2.97
15	105	3.26	104	3.13	103	3.05
16	107	3.39	105	3.24	104	3.15
17	108	3.49	107	3.31	105	3.24
18	110	3.60	108	3.39	107	3.33
19	112	3.73	110	3.52	108	3.44
20	114	3.86	113	3.66	110	3.55
21	116	3.96	115	3.81	112	3.66
22	119	4.07	117	3.95	114	3.77
23	122	4.26	119	4.07	116	3.89
24	124	4.45	122	4.20	118	4.01
25	128	4.62	124	4.34	120	4.10
26	131	4.80	126	4.47	122	4.20
27	135	4.98	130	4.61	124	4.38
28	138	5.17	133	4.80	127	4.55
29	142	5.36	135	4.94	130	4.68
30	146	5.55	138	5.09	133	4.81
31	150	5.77	141	5.27	136	4.94
32	154	5.97	144	5.46	139	5.11

treated every treatment day. The total tumor dose in most cases is 4,600 r over a period of 30 to 32 days.

The calculation of the time in which to give the required dosage is made easier by the use of the Treatment Time and "Skin" Dosage Charts[12] for 80 cm. source skin distance. Such a chart for the period from October 1, 1960 to December 31, 1960 is shown in Table I. In order to deliver 100 r to the midplane of the supraclavicular-axillary field, the thickness of which is 14 cm. with an average area of approximately 200 sq. cm., look at column 1 for a thickness of 14 cm., then follow this line to column 5, where it is seen that the time required to give 100 r from the two opposing fields is 3.03 minutes. The maximum or "skin" dose (really 6 mm. beneath the skin) for this time is 102 r. Since our daily midplane dose is 200 r, the time required to give this dose for each of the two opposing ports is 6.06 minutes. The "skin" dose or maximum will then be 204 r. The exit dose is taken into account in the calculation of this table.

The time required in treating the tangential ports is calculated in the same way. To give 100 r to the midplane, look at column 1 for a thickness of 31 cm. and then follow this line to the 200 sq. cm. column. The time shown is 5.27 minutes for each of the two opposing ports. For 200 r the time will be 10.54 minutes for each port. The maximum dose at the planes of entrance and exit will be 282 r. Because the dose varies from point to point along the tangential field, we record only the midplane dose for the two opposing tangential fields.

Sometimes the anterior supraclavicular-axillary field is greater transversely than the largest field obtainable with our machine at a source skin distance of 80 cm. When this occurs we treat the anterior supraclavicular-axillary port at a source skin distance of 100 cm.

ISODOSE CURVES

The dosage distribution in per cent of tumor or midplane dose for the two opposing supraclavicular-axillary ports is given in Figure 8. This distribution holds only when the fields are bolused with unit density material so that the thickness is uniform throughout. The dosage distribution is uniform and ranges from 103 per cent near the surface to 100 per cent at the midplane. For the "average" patient only the apex of the lung is exposed within the 100 per cent isodose area, other portions between the 80 per cent and 100 per cent isodose regions.

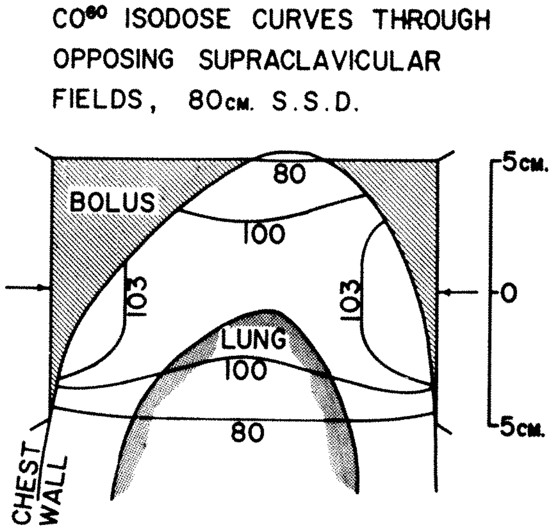
CO60 ISODOSE CURVES THROUGH OPPOSING SUPRACLAVICULAR FIELDS, 80CM. S.S.D.
BOLUS
80
100
103
103
LUNG
100
80
CHEST WALL
5CM.
0
5CM.

Fig. 8. Co^{60} isodose curves for two opposing supraclavicular-axillary fields at a source skin distance of 80 cm., showing per cent of midline dose.

The isodose curves for the two opposing tangential ports are shown in Figure 9 for a separation of 26 cm. and 10×15 cm. fields at 80 cm. source skin distance. In the lower half the per cent of the tumor dose at the midplane is given. Here, there is a variation from 100 per cent at the midplane to 135 per cent at the extreme edge of the tangential fields.

These isodose curves, as those for the supraclavicular-axillary field, hold only if the space between the two tangential fields is bolused. Without the bolus large areas may be overdosed because there is no overlying absorbing material, while the immediate surface area may be underdosed because there is a lack of build-up material to obtain the maximum on the skin. Here

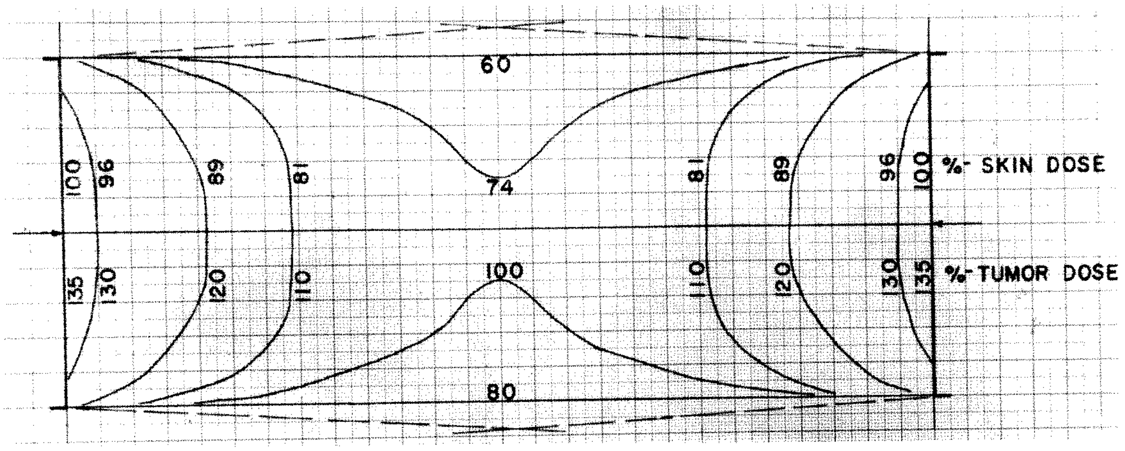

Fig. 9. Co^{60} isodose curves for two opposing tangential ports 26 cm. apart at a source skin distance of 80 cm., 10×15 cm. fields showing per cent of skin dose and per cent of tumor dose.

the skin-sparing effect due to build-up is unwanted if the scar area and the possible skin involvement is to receive the maximum dose.

The isodose distribution on the chest area of a patient is shown in Figure 10. The internal mammary lymph nodes are schematically located in the extreme position of 5 cm. from the midline and 2 cm. deep; the edge of the field is just past the contralateral lymph node.

VERIFICATION RADIOGRAPHS

In order to assay how much lung tissue is being irradiated, radiographs are exposed with the cobalt apparatus set up as for treatment. We use Kodak Blue Brand film in a cardboard cassette, reversed so that the lead side faces the radiation. The first exposure is made for the treated port, exposing the film for $^4/_3$ r. The diaphragm is then opened wide without changing the position of the patient or the film, and the film is exposed a second time for $^2/_3$ r. Figure 11 is a verification radiograph, as we call it, of the anterior supraclavicular-axillary port. The darker area is that of the treated port. The larger port shows the relationship of the treated port to the surrounding area. Notice that the apex of the lung is included in the treated field.

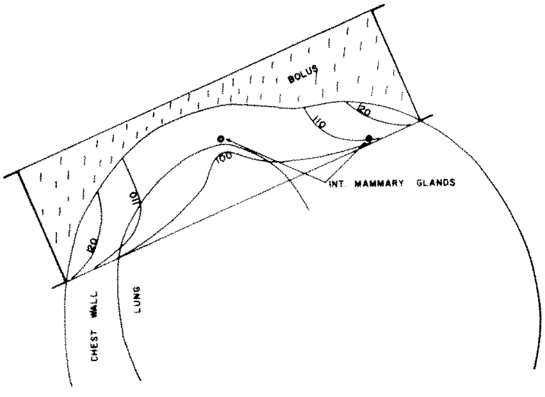

Fig. 10. Isodose distribution for two opposing tangential ports on the breast area of a patient.

Figure 12 shows a verification radiograph of the medial tangential field. Only a small section of the lung is included in this field.

STAGING

Patients who are referred for radiation therapy are generally the advanced cases, as can be seen from Table II. Seventy per cent of our cases were in Stages III and IV, according to the Manchester System of classification.

OPERATIVE PROCEDURES

In Table III are listed the operative procedures. About 65 per cent of our patients had a radical mastectomy. Generally, when no mastectomy or a simple mastectomy was performed, it was because the disease was too extensive. It is interesting to note that 7 per cent had double mastectomies.

TABLE II

STAGING OF PATIENTS

Stage	Living		Deceased	
	No.	Per Cent	No.	Per Cent
I	6	9	6*	13*
II	20	31	0	0
III	21	32	15	32
IV	18	28	26	55
Total	65	100	47	100

* Five of these died without disease, 4 of "heart disease" and 1 was a suicide.

STATUS OF PATIENTS

An analysis of the status of our patients as of May 1, 1962 is given in Table IV. Some of these were treated too near this date to allow for a good evaluation. With this reservation in mind, 42 per cent of our patients are deceased and 58 per cent are living. Of the living, about one-fourth have persistent disease.

RESULTS

Most of our results are based on the examination of 112 patients, treated from April, 1957 to March, 1962, for whom we have a complete follow-up. Twelve more cases have been lost to follow-up and have not been counted in our statistics except in those pertaining to skin nodules.

TABLE III

TYPE OF MASTECTOMY

	No Mastectomy[1]	Simple Mastectomy[2]	Radical Mastectomy	Double Mastectomy
	In Living Patients			
No.	5	9	47[3]	5
Per Cent	8	14	72	8
	In Deceased Patients			
No.	11	9[4]	25	3
Per Cent	23.4	19	53	6.4

[1] Of 16 cases without mastectomy 15 were Stage III or Stage IV.

[2] Of 18 cases with simple mastectomy, 12 were Stage III or Stage IV.

[3] One patient is included in the radical mastectomy and double mastectomy group.

[4] Patient first had a simple mastectomy, later the other breast was removed; therefore, she is counted twice.

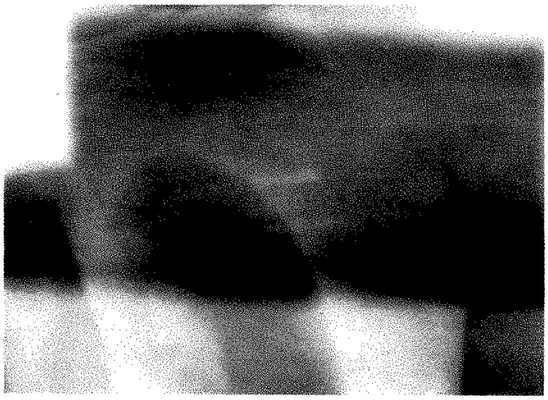

FIG. 11. Verification radiograph of anterior supraclavicular-axillary port.

SKIN REACTION

The patient is given a sheet of instructions on the care of the skin. She is asked not to wet or oil the areas being treated, to

FIG. 12. Verification radiograph of medial tangential port.

TABLE IV

STATUS OF PATIENTS

	Living		Deceased		Total	Lost to Follow-up
	With Disease	Without Disease	With Disease	Without Disease		
No.	18	47	39	8*	112	12
Per Cent	16	42	35	7		
	58%		42%		100%	

* Five of the 8 who died with no disease were in Stage I. The cause of death in all but one was cardiovascular accident.

air the treated sites frequently and to avoid irritation and friction. Some patients showed little reaction. In most cases by the end of treatment there was a moderate skin reddening which usually changed into a dry desquamation. The skin healed rapidly, clearing in 3 to 4 weeks. We have not seen any severe skin reactions.

PULMONARY CHANGES DUE TO THERAPY

Pulmonary fibrosis following radiation therapy has long been recognized and often described.[6,29,13,30,2,17] The tissue changes in the pulmonary structures are chiefly those of an inflammatory reaction. First there is edema, then cellular congestion and desquamation of bronchial and alveolar cells, then clearing by absorption and, finally, regeneration. In mild reactions there usually is complete clearing of exudate with no resultant abnormality of structure. In more severe and extensive injury, the healing pattern varies. Clearing and absorption occur but a final fibrosis of substitution follows in the more heavily irradiated tissues. All these changes are dependent on the condition of the patient at the time of radiation therapy; age, arteriosclerosis, previous lung disease, ischemia and metastases are influencing factors. Only rarely does a patient exhibit clinical symptoms such as cough, chest pain and dyspnea after therapy.

A small drop in vital lung capacity may occur. Gish *et al.*[5] found no significant change following breast radiation therapy. When there was a change in vital capacity, it was usually associated with pulmonary metastases. When a significant drop in vital capacity occurs, the spread of disease rather than radiation pleuropneumonitis should be suspected.

A study was made of pulmonary changes and the time of their appearance by taking chest roentgenograms of patients $1\frac{1}{2}$ months, 3 months, 5 months, 7 months, 9 months, 12 months and every 6 months thereafter, after completion of therapy. Of 62 cases having a complete series of roentgenograms, 75 per cent exhibited evidence of some pulmonary change in the region of the two opposing supraclavicular-axillary ports. Figure 13 shows the changes in the right upper lobe found in an average case 2

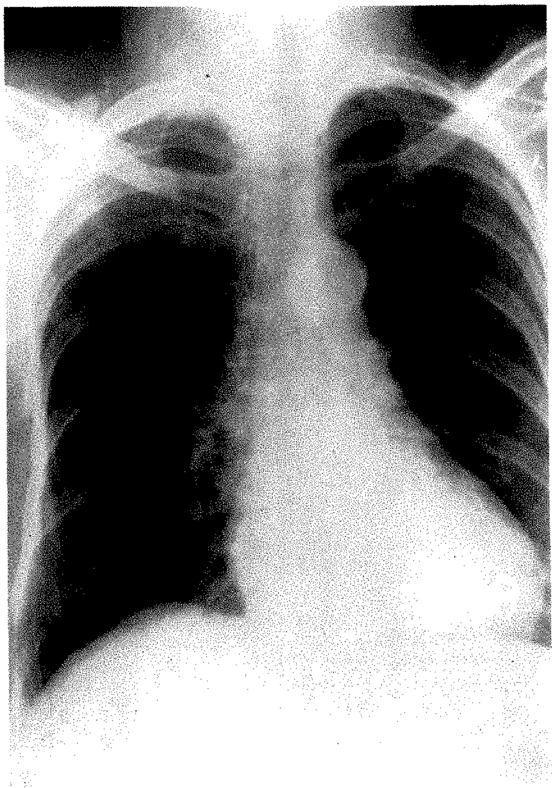

FIG. 13. Roentgenogram of the chest taken 2 months after therapy showing the average radiation changes in the right upper lobe in the region of the two opposing supraclavicular-axillary ports.

months after therapy. The lung changes were graded as (1) just recognizable, (2) mild and (3) moderate. Sixty-five per cent of the cases fell in the first two grades. In no case was there a severe change.

Specific roentgenographic changes were first recognized outside and above the hilar site. In almost all cases there were connecting linear densities to the hilus. Early shadows were rather diffuse, hazy and ill-defined, occupying only a segment of lung tissue. They were rectangular in outline and positioned in an oblique direction from the hilus up and outward, rarely measuring more than 3 cm. in width. Often, the very apex of the lung was not occluded.

The distribution of the time of the initial appearance of a change is shown in Figure 14. The greatest number of pulmonary changes appeared between 1½ and 3 months after therapy. By 5 months about 80 per cent of all the pulmonary changes were evident. In a few cases, the initial changes appeared as late as 1½ to 2 years after therapy. Of the 46 positive cases, 7 or 15 per cent became negative within 1 year to 3 years post-therapy. Only 1 patient had symptomatic evidence of pulmonary reaction.

There was no roentgenographic evidence of any pulmonary change in the region of the tangential ports.

From this study it is concluded that the possible occurrence of pulmonary changes should not be considered a deterrent to postmastectomy radiation therapy.

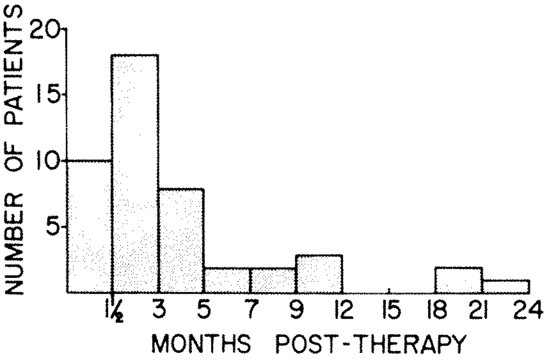

Fig. 14. Time of initial appearance of pulmonary change in the apex of the lung treated through two opposing supraclavicular-axillary ports to a dose of approximately 4,600 r.

EFFECT ON METASTATIC LYMPH NODES

There is a great deal of evidence that metastatic lymph nodes from breast carcinoma can be sterilized or confined. Mc Whirter[19] has described the radiation responsiveness of positive lymph nodes. He believes that these structures are more readily controlled by radiation therapy than the primary breast lesion. Lenz[14] has shown that confinement of carcinoma to these structures occurs with doses above 4,000 r. Whether carcinoma cells are sterilized or made locally inactive by entrapment and encirclement may not matter as long as spread or reactivity from these sites is prevented. There is an appreciable number of patients with lymphedema of the arm due to metastatic disease in the axillary lymph nodes. With radiation therapy the lymph nodes are often controlled, with resultant decrease in edema.

In our series, 16 or 25 per cent of the living patients had lymph node metastases at the beginning of radiation therapy. In 7 cases the metastases had disappeared before the end of therapy and in 2 before the end of 1 year after therapy, so that 9 cases of 16 or 56 per cent were controlled. In the deceased group there was an incidence of positive lymph node disease at the beginning of therapy in 43 per cent of the patients; in 35 per cent the disease was controlled by 1 year after therapy (Table v).

Since our figures show that positive palpable axillary-supraclavicular or cervical lymph node metastases were controlled without further evidence of activity in 45 per cent of the cases, one may assume a similar effect on the internal mammary lymph nodes. Because of this, it is felt that proper treatment should include irradiation of all possible locations of disease.

Here, too, we would like to emphasize that a bolus should be used over the lymph nodes which are within 0.5 cm. from the surface of the skin. Placing bolus in the axillary region produces a uniform dose

Table V

EFFECT OF RADIATION THERAPY ON METASTATIC LYMPH NODES

	Lymph Nodes Present at Beginning of Therapy	No. of Cases Showing Lymph Node Clearing		Per Cent of Cases Showing Lymph Node Clearing
		By End of Therapy	By 1 Yr.	
	In Living Patients			
No.	16	7	2	
Per Cent	25			56
	In Deceased Patients			
No.	20	5	2	
Per Cent	43			35

through the axillary lymph nodes and avoids under dosing of those lymph nodes near the surface.

ARM EDEMA

Arm edema has been attributed to many causes. Some studies suggest that infection in the axilla and arm is of primary importance. Other contributing factors are late fibrosis after surgery or radiation therapy, and obstruction of the axillary vein. Lymphedema following radical mastectomy has always been a surgical problem. With recent improved surgical techniques and antibiotics, this incidence has not been lowered. The occurrence varies between 12 per cent[8] and 57.5 per cent.[23] Hoopes and McGraw,[11] Holman *et al.*,[10] Guthrie and Gagnon,[7] and Haagensen[8] support the view that infection plays a major role in causing either early or late edema. Devenish and Jessop,[3] Rienhoff,[22] and Standard[24] feel that surgical interference with the lymphatic vessels is the principal cause of arm edema. On the other hand, Veal[26] attributed arm edema in 90 per cent of his patients to venous obstruction; yet, Mac Donald[16] and Lobb and Harkins[15] cited 70 cases in which part or all of the axillary vein was resected without development of significant edema. Holman *et al.*[10] and Lobb and Harkins[15] stressed the relationship of weeping radiodermatitis to subsequent lymphedema.

We recorded as arm edema any visible increase in the affected side over that of the normal side. Twenty-six per cent of the surviving patients had arm edema at the beginning of therapy. In one-third of the cases this disappeared by the end of therapy. However, arm edema appeared in 28 per cent of the cases by 2 months after therapy where there had not been any before therapy (Table VI). If the arm edema before therapy was not severe, that which followed therapy was also mild. In our experience lymphedema did not prove to be a frequent or disabling sequela of radiation therapy.

METASTASES

Of 122 cases analyzed, 14 or 11.5 per cent had skin nodules which appeared during or after therapy: 5.7 per cent in the treated site, 2.5 per cent outside the treated area

Table VI

INCIDENCE OF ARM EDEMA BEFORE AND AFTER THERAPY

	Present at Beginning of Therapy	At End of Therapy		Not Present Before But Appeared After Therapy		Per Cent Incidence
		Regressed	Persisted	1 Mo. Post Therapy	2 Mo. Post Therapy	
		In Living Patients				
No.	17	6	11	4	14	
Per Cent	26	35	65	6	22	54
		In Deceased Patients				
No.	8		8	1	1	
Per Cent	17		100	2	2	21

and 3.3 per cent both within and outside the treated sites. About half of those which appeared in the treated site appeared only on the scar line. In the treated area the initial appearance of skin nodules was from 2 to 36 months after therapy, while in the untreated areas the initial appearance was from any time during therapy to 16 months after therapy.

The incidence of lung metastases was 11 per cent for the surviving patients and 13 per cent for the deceased, with an average of 12 per cent for both groups (Table VII).

The incidence of metastases in bone was 17 per cent for the living group and 36 per cent for the deceased group, with an average of 25 per cent for both groups. This is shown in Table VIII.

SURVIVAL RATE

It is too early in our study to give 5 year survival results; however, it might be informative to show the survival time of deceased patients in order to evaluate palliation. This is given in Table IX. More than half of these patients died within the first year and more than 90 per cent within 2 years.

DISCUSSION

A philosophy of treatment on which radiation therapy is based is necessary. Our aim is to sterilize or confine any viable cancer cells lodged in the local lymph nodes or chest wall. With our technique we are able to deliver a tissue dose of 4,600 r, considered to be effective.

The local recurrence of skin nodules in the treated site for unselected cases was 9 per cent, which is lower than the 15 to 41 per cent[4,20,21] given in the literature. Another important factor is the delay in the appearance of skin nodules by as much as 2 years as compared to that in untreated areas. With our method of therapy, known palpable axillary lymph nodes have been cleared in 45 per cent of the cases. Whether our survival rate will be better than that of others remains to be seen. Thus far 42 per cent of our patients are alive without known disease and 16 per cent with disease. It is our impression that greater palliation with less discomfort is achieved by this method since in only 1 patient was there symptomatic evidence of lung reaction.

Table VII

INCIDENCE OF LUNG METASTASES

Living		Deceased		Total	
No.	Per Cent	No.	Per Cent	No.	Per Cent
7	11	6	13	13	12

Table VIII

INCIDENCE OF BONE METASTASES

Living		Deceased		Total	
No.	Per Cent	No.	Per Cent	No.	Per Cent
11	17	17	36	28	25

If effective therapy can be administered without any morbidity or sequelae with a particular technique, it may be ordered routinely on all postoperative cases. The postirradiation changes most feared in treating breast carcinoma, skin ulcerations and fibrosis, increased arm edema and pulmonary fibrosis, have not developed in our series to any significant degree. Skin changes never became a problem. Arm edema is a frequent complication of radical

Table IX

SURVIVAL TIME AFTER THERAPY OF DECEASED PATIENTS

	Months					
	1	2–3	4–6	7–12	13–24	>24
No.	3	8	5	11	16	4
Per Cent	6.4	17	10.7	23.4	34	8.5
	← 57.5% →					
	← 91.5% →					

mastectomy with and without radiation therapy. We found that 28 per cent of patients who did not have arm edema at the beginning of radiation therapy developed it within 1 year after therapy. This was never severe and did not produce a poorly functioning arm. The fact that no wet radiodermatitis occurred in the axilla may be an important aspect of this mode of treatment since infection is a great causative factor in lymphedema.

In our follow-up with roentgenograms of the chest, we have established that a pulmonary reaction can be prevented under the tangential portals while delivering an effective dose to the internal mammary lymph chains, the chest wall and adjacent pleural structures. As is seen from the verification radiographs only a small segment of the peripheral lung tissue is irradiated. The pleura never showed thickening, nor did pleural effusion occur under these sites. When pleural effusion did occur in our cases, it was always associated with pleural metastases. It should again be emphasized that a bolus must always be used over these ports in order to deliver a calculated dose to all of the exposed tissues.

Our study showed that only in the apical portion of the lung was there a recognizable reaction to radiation therapy. This site was within the opposing anteroposterior axillary-supraclavicular portals. Some distinguishable change was evident in 75 per cent of the patients. The greatest frequency of initial occurrence of pulmonary reaction was 3 months after therapy, although in 22 per cent occurrence was noted during the first 1½ months. Follow-up established that in 80 per cent the pulmonary changes in the lung apices occurred within 5 months but may occur as long as 2 years after therapy. Fifteen per cent of the positive cases became negative in 1 to 3 years after therapy. With the exception of 1 case, no post-therapy symptoms were encountered.

With this method we have found that an effective tissue dose can be administered to all patients who are inoperable or who have had simple or radical mastectomies with no disabling sequelae. In patients who have had mastectomies, radiation therapy should be started 2 to 4 weeks after operation since a delay may make such treatment less effective.[27]

SUMMARY

1. A modified McWhirter technique for the treatment of breast carcinoma with cobalt 60 teletherapy has been described.

2. Isodose curves are given for the two opposing supraclavicular-axillary ports and for the two opposing tangential chest fields.

3. The method of taking verification radiographs using Co^{60} radiation is described.

4. Tables are given listing the stages of the disease, the type of mastectomy, the incidence of arm edema, the status of living patients and the survival time after therapy of deceased patients.

5. Radiation therapy proved effective in clearing metastatic lymph nodes in 56 per cent of the surviving patients and in 35 per cent of the deceased patients in our series.

6. The incidence of skin metastases, bone metastases and lung metastases is given.

7. A bar graph showing the incidence of a barely perceptible pulmonary change versus the time of appearance after therapy is given for the two opposing supraclavicular-axillary ports. In 75 per cent of the cases such a change occurred. Eighty per cent of these patients showed such changes by 5 months after therapy. No pulmonary changes in the region of the two opposing tangential chest ports were noted.

8. The clinical significance of the reactions for this method of therapy is discussed.

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MASSIVE DOSE TECHNIQUE IN RADIATION THERAPY OF INOPERABLE CARCINOMA OF THE BREAST*

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OBSERVATIONS of normal tissue and tumor cell recovery after irradiation indicate the value of protraction in treating squamous cell carcinoma of the skin.[3] The more rapid recovery of the skin results in an improved therapeutic ratio when over-all treatment time is carried out beyond 2 weeks in many equal fractions. The studies of Cohen[2] and Friedman and Pearlman[5] suggest that the same situation does not hold true for adenocarcinoma of the breast. The recovery rate for radiation damage to the skin and tumor are about the same and therefore no advantage is to be gained by prolongation of the treatment course.

Cochran *et al.*,[1] utilizing the data obtained by the above investigators, instituted a study of patients with advanced breast carcinoma. They treated the primary tumor, chest wall and regional lymph nodes to a dose as high as 2,500 r in 2 consecutive days. Only preliminary results have been published.

A similar study was instituted at the Columbia-Presbyterian Medical Center as part of a larger project to investigate the effects of unconventional fractionation techniques.[7] Two groups of patients were selected for this study: (a) Stage III (12 cases) consisting of patients with breast carcinoma inoperable due to involvement of the highest axillary lymph node, supraclavicular lymph nodes or internal mammary lymph nodes; and (b) Stage IV (5 cases) consisting of patients with widespread metastatic tumor who had extensive primary tumors requiring therapy.

The study was terminated early in 1962 because of a rather high incidence of complications. This report represents a minimum follow-up of 18 months and a maximum of 34 months.

METHOD

In Stage III patients, a pattern of definitive radiation fields was used to encompass all known extent of the cancer. Opposing tangential fields, 10×15 cm. or 12×15 cm., were used to irradiate the breast, chest wall and ipsilateral internal mammary lymph nodes. An anterior 12×20 cm. field was applied to cover the axillary, supraclavicular, subclavicular and lower cervical lymph nodes. Treatment was given on the 22.5 mev. betatron with the roentgen-ray beam. Water bolus was used between the tangential chest wall portals and 2 cm. lucite as bolus was used for the supraclavicular portal. A triangular lead shield protected the trachea.

As a rule, smaller volumes of tissue were treated in the Stage IV patients. The attempt in these cases was to treat only the primary lesion except in 1 instance where the primary, regional lymph nodes and mediastinum were all included in the treatment fields and another where the supraclavicular portal was also included.

The total dose of 2,500 r to the skin and tumor was delivered in two fractions a week apart. The distribution of dosage is very homogeneous with the betatron beam. The radiation dose to the primary tumor, regional lymph nodes and skin did not vary more than about 10 per cent. Where two separate volumes such as chest wall and supraclavicular lymph nodes were treated, both might be irradiated within the same calendar week but the total dose to any one tumor volume was delivered in an elapsed time of 1 week.

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RESULTS

IMMEDIATE REACTIONS

Because of the low dose rate at the distance required to encompass the necessary field sizes on the betatron, many of the patients complained of transitory ache in the arm or shoulder after maintaining the treatment position for 35 to 45 minutes. This disappeared within several hours. Two patients complained of some anorexia or nausea the evening of, or the day following, treatment. These symptoms are difficult to evaluate but the remainder of the patients were free of any pronounced systemic complaints secondary to the irradiation.

SKIN REACTIONS

The radiation epidermitis was, on the whole, less severe than in those patients treated in the usual manner with 5,000 r maximum skin dose in 4 weeks. Erythema first appeared as early as 4 days and as late as 19 days, the average being 7 to 8 days. This progressed to a maximum reaction in 3 to 4 weeks after completion of irradiation. This maximum reaction consisted of dry desquamation except in 5 instances where a moderate moist epidermolysis was apparent. The skin reaction had completely subsided by at least 8 weeks in all cases.

ESOPHAGITIS

Esophagitis was secondary to inclusion of the lower cervical esophagus toward the edge of the supraclavicular field. Esophagitis was experienced in 9 of the 14 patients treated with this field. In 2 cases this was severe and resulted in moderate weight loss before the reaction subsided. In another case, esophagitis was moderately severe. In 1 additional case, late esophagitis with narrowing of the lumen was observed as part of a complex of late reactions which will be described in detail below.

LATE COMPLICATIONS

Late complications were mainly of three types; pulmonary fibrosis, fibrosis of the pectoralis musculature and myelitis of the lower cervical and upper thoracic spinal cord. Pulmonary changes were initially seen on roentgenograms in the apex of the irradiated side from $1\frac{1}{2}$ to 6 months post treatment. The changes were asymptomatic in all cases and were again presumably secondary to the inclusion of this region by the supraclavicular fields. This complication was noted in 9 of 14 patients who had this region included in their irradiated volume.

A serious and common complication was the fibrosis of the pectoralis musculature which occurred in all of the 11 patients classified as Stage III who survived more than 5 months. One patient, who died of metastases at 5 months postirradiation, was not noted to have this complication. The onset of fibrosis with limitation of arm movement in abduction was noted at 4 to 11 months after completion of therapy, in most of the cases occurring at 4 to 6 months. Fibrosis was often associated with edema of the upper chest wall and mild edema of the breast itself.

One patient (Case III) with persistent pain and limitation of motion of the shoulder joint on the irradiated side was discovered to have, in addition to severe fibrosis, roentgenographic evidence of humeral head radionecrosis (Fig. 4 and 5).

Another patient (Case I) suffered a whole gamut of radiation complications and eventually died 18 months following treatment of radiation myelitis. Her reactions seemed to indicate that she was unusually sensitive to irradiation. Two other patients developed radiation myelitis, 1 at 19 months and the other at 30 months following irradiation. In both of these patients the condition appeared to stabilize about 3 months after onset of symptoms of myelitis.*

TUMOR CONTROL AND SURVIVAL

Tumor response, both of the primary and regional lymph nodes, was generally excellent (Table I). Of the 12 Stage III patients, only 1 patient was definitely not controlled and required radioactive iridium seed implantation and finally a simple mastectomy. A second patient was only partially controlled. The breast mass which was

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* Since this report was submitted for publication one additional patient has developed radiation myelitis.

TABLE I

RESULTS OF THERAPY IN STAGE III PATIENTS

Patient	Tumor Control	Survival	Esophagitis	Pulmonary Fibrosis	Pectoralis Fibrosis	Other Complications
E.S.	5 mo. partial	Dead at 5 mo. of metastases	severe	no	no	none
V.deP.	34 mo. complete	Living without clinical disease at 34 mo.	moderately severe	yes	yes	myelitis, necrosis of humeral head, vocal cord paresis
F.G.	12 mo. complete	Dead at 12 mo. of metastases	mild	yes	yes	none
C.T.	18 mo. complete	Dead at 18 mo. of radiation myelitis. No cancer found at autopsy	moderate	yes	yes	myelitis, esophageal strictures, vocal cord paralysis
D.B.	23 mo. complete	Living without clinical disease at 23 mo.	severe	yes	yes	myelitis
M.W.	22 mo. complete	Living without clinical disease at 20 mo.	mild	yes	yes	none
A.V.	20 mo. complete	Living without clinical disease at 22 mo.	no	yes	mild	none
I.B.	19 mo. complete	Living without clinical disease at 19 mo.	mild	yes	yes	none*
K.M.	not controlled by radiation	Living after mastectomy at 19 mo.	no	no	yes	none
E.R.	18 mo. complete	Living without clinical disease at 18 mo.	mild	no	yes	none
F.R.	18 mo. complete	Living without clinical disease at 18 mo.	no	yes	yes	none
I.G.	9 mo. partial	Dead of metastases at 14 mo.	no	no	yes	none

* Developed myelitis after report was submitted for publication.

TABLE II

RESULTS OF THERAPY IN STAGE IV PATIENTS

Patient	Areas Treated	Complications	Tumor Control	Survival
B.M.	Breast and chest wall	none	not controlled	dead at 8 mo. with metastases
I.deO.	Both breasts	none	partial 6 mo.	dead at 15 mo. with metastases
C.H.	Breast, chest wall and regional lymph nodes	pulmonary fibrosis	not controlled	dead at 4 mo. with metastases
E.L.	Breast mass only	none	partial 19 mo.	dead at 19 mo. with metastases
I.D.	Breast, chest wall, regional lymph nodes and mediastinum	none	complete local control 6 mo.	dead at 6 mo. with metastases
T.C.	Breast	none	complete local control 3 mo.	dead at 3 mo. with metastases

9×11 cm. shrank to 7 cm. in diameter for 9 months but started to re-grow accompanied by distant metastases, then responded to prednisone; however, the ascites remained uncontrolled and the patient expired 14 months following initial therapy.

Three other patients have died, 1 at 18 months of radiation myelitis but without tumor at autopsy (Case 1); another with metastases 5 months after therapy, with marked reduction but not complete disappearance of a 7×8 cm. mass; and a third patient expired at 12 months of exsanguinating hemoptysis secondary to mediastinal and tracheal involvement by carcinoma, the previously treated primary site remaining clinically free of tumor.

The remaining 7 patients are clinically free of tumor from 18 to 34 months following therapy. Of these patients, 5 were postmenopausal and had no other hormonal alteration. One 57 year old postmenopausal woman and a 42 year old premenopausal woman had oophorectomies prior to radiation therapy. It is impossible to judge the effect of this procedure on the results.

In all, it can be said that 9 patients were completely controlled at the irradiated site, 2 were partially controlled and 1 not controlled.

The response in the Stage IV patients was somewhat less satisfactory (Table II). Two patients had complete control of the primary site but died at 3 and 6 months, respectively, of advanced metastatic disease. Two patients were partially controlled for 6 and 19 months, respectively. The latter patient had a threatening ulceration of the skin by a 10 cm. round mass in the breast. This regressed to a 6 cm. round mass and the patient also responded temporarily to estrogen and then male hormone therapy, but finally succumbed to widespread bone and soft tissue metastases.

Two of the Stage IV patients did not respond. They had widespread and rapidly progressive disease of the breast and skin of the surrounding area.

REPORT OF CASES

CASE I. P.H. #98-53-96 (C.T.). This 44 year old Negro female was admitted to the Colum-

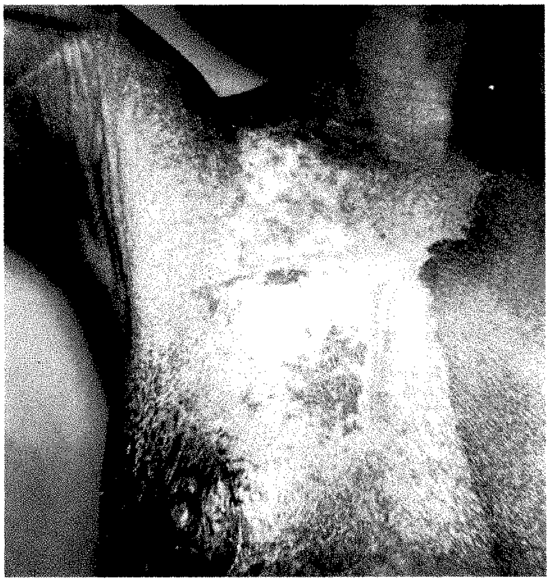

FIG. 1. Case 1. Two months following completion of radiation therapy. Dry desquamation of breast and chest wall has essentially cleared. Early atrophic changes are present in the subclavicular area. Abduction of arm is nearly normal.

bia-Presbyterian Medical Center on December 27, 1960, because of a lump in the right breast of 10 days' duration. There was no history of trauma or discharge. She had previously nursed 2 children without difficulty.

Physical examination revealed a 2×2 cm. firm discrete subareolar mass just inferior and medial to the nipple. A single 1 cm. lymph node was palpable in the right axilla. Skeletal survey, chest roentgenograms and other laboratory data were all normal.

A triple biopsy of the primary lesion, highest axillary lymph nodes and the 1st, 2nd and 3rd intercostal lymph nodes of the internal mammary chain was done on December 31, 1960. All specimens showed poorly differentiated carcinoma. The perivascular lymphatic spaces about the primary breast lesion were infiltrated with tumor cells.

Radiation therapy to the primary lesion, chest wall, axilla, supraclavicular area and ipsilateral internal mammary lymph node chain was begun on January 10, 1961. Two tangential portals with water bolus to the chest wall and a single direct anterior supraclavicular and axillary 12×20 cm. portal were used, treatment being given by the 22.5 mev. roentgenray beam of the betatron. The total dose to all areas was 2,500 r maximum to the skin and tumor, given in two equal fractions 1 week apart.

Following radiation therapy, the patient had moderate dysphagia and a dry desquamation of the skin in the areas irradiated. The reaction had essentially cleared by February 14, 1961. The breast mass had completely disappeared by March 14, 1961, but at that time rather marked late skin changes secondary to irradiation were noted along with some limitation of motion of the right arm (Fig. 1).

There was never any evidence of recurrent carcinoma after that date. However, the fibrosis of tissues of the chest wall, supraclavicular areas and about the shoulder joint progressed to produce severe limitation of motion which was never relieved. A chest roentgenogram 7 months following radiation therapy showed minimal apical pulmonary fibrosis on the treated side.

Progressive sore throat and difficulty in swallowing were noted in September, 1961 and an esophagram showed a stenotic cervical esophagus. Esophagoscopy on November 17, 1961, revealed a stricture and fibrosis of the cervical esophagus; a biopsy showed no evidence of malignancy. The vocal cords were normal at this time.

Late in November, 1961, the patient first had signs of numbness and diminished heat sensation of the left leg as far up as the groin. She was admitted to the Neurological Institute of the Columbia-Presbyterian Medical Center on December 8, 1961. Neurologic examination revealed diminished pain sensation from the toes to the hip on the right and absent pain sensation of the left lower extremity. Temperature sensation was also abnormal. Skeletal survey, lumbar puncture and myelogram were all within normal limits. The diagnosis, by exclusion, was radiation myelitis.

The patient was discharged December 16, 1961 only to be readmitted the next day on the Otolaryngological Service because of respiratory distress and weakness of the voice. It was noted that she had fixation of the left vocal cord and decreased motion of the right vocal cord. Edema of the epiglottis and arytenoids was present. An emergency tracheostomy was performed and the laryngeal edema diminished on conservative therapy over the next 5 days. No cause was found to account for this episode. The tracheostome was allowed to close and both vocal cords were noted to move well 9 days after the initial episode.

The neurologic signs progressed steadily with involvement of the muscular innervation of the right lower extremity. The patient was readmitted to the Neurological Institute on April 18, 1962, because of increasing weakness of both lower extremities and the right arm. The sensory examination localized the level at T3 on the left side. The Brown-Sequard syndrome progressed and the patient expired on July 11, 1962.

Autopsy revealed severe radiation myelitis of the lower cervical and upper thoracic spinal cord. No evidence of tumor could be found anywhere in the body.

CASE II. P.H. #99-53-54 (A.V.). The patient, a 65 year old white woman, was admitted to the Columbia-Presbyterian Hospital on September 11, 1961, because of early gangrene of the right foot associated with diabetes mellitus and peripheral vascular disease. On initial work-up, a breast mass was discovered which the patient later admitted had been present 3 years. In the patient's past history, a diagnosis of Laennec's cirrhosis had been established in 1950, at which time a hysterectomy and bilateral oophorectomy were performed for leiomyomata uteri. Diabetes mellitus was diagnosed in 1951 and the patient intermittently followed a diabetic diet until the present admission.

Physical examination revealed a right breast mass measuring 4×5 cm. just medial to and above the areola and fixed to the overlying skin. A single firm 1 cm. axillary lymph node was present on the right side. The liver was enlarged to 3 cm. below the right costal margin and the spleen tip was palpable on the left side. Erythema and edema with some induration were noted involving the 2nd, 3rd and 4th toes of the right foot.

Laboratory studies revealed: fasting blood sugar 242 mg. per cent, urine glucose 2+, hemoglobin 14.0 gm., white blood cell count 7,300. A skeletal survey showed no evidence of metastases. A radioactive colloidal gold liver scan showed cirrhosis with a suspicion of metastasis, but no change was noted 15 months later on repeat scan.

A triple breast biopsy on September 25, 1961, revealed duct-cell carcinoma with prominent fibroblastic reaction involving the breast and the first and second intercostal space lymph nodes of the internal mammary chain. No tumor was seen in the highest axillary lymph nodes.

Treatment of the vascular disease involving the toes was conservative and gradual improvement was noted. Radiation therapy was instituted for the breast lesion on October 3, 1961. A maximum skin dose (and tumor dose) of 2,500 r, divided in two fractions a week apart, was delivered through two opposing tangential ports to include the breast, chest wall and ipsilateral internal mammary lymph nodes. A direct 12×20 cm. portal covered the axilla and supraclavicular lymph nodes. All treatment was given with the 22.5 mev. roentgen-ray beam of the betatron.

Response was excellent, with a moderate dry skin reaction and disappearance of palpable disease by 1 month after completion of therapy. Repeat roentgenograms 1 year later showed right apical pulmonary fibrosis, but no evidence of metastasis. Slight stiffness of the right shoulder was present and there was mild edema of the breast. The patient was last seen 20 months following radiation therapy without clinical evidence of the breast tumor or metastases.

CASE III. P.H. #148-48-81 (V. deP.). This 63 year old Negro woman was admitted to the Columbia-Presbyterian Medical Center on July 16, 1960, because of a lump in the right breast of 3 weeks' duration. The lump had been "needled" a week prior to admission by the family physician but no fluid was obtained. There was no pain or nipple discharge. The patient was 13 years postmenopausal.

Physical examination revealed a 3×4 cm. hard, irregular mass in the upper outer quadrant of the right breast. Retraction of the skin over the lesion was noted. Two right axillary lymph nodes, 2.0 cm. and 1.5 cm. in diameter, were palpated. Skeletal survey and laboratory studies were within normal limits.

Triple biopsy was performed on July 18, 1960. A scirrhous carcinoma was found at the primary site and involving the highest axillary lymph nodes. The internal mammary lymph nodes were not involved with tumor.

Radiation therapy was started on July 26, 1960. A maximum skin and tumor dose of 2,500 r was delivered in two equal fractions spaced 1 week apart to the primary lesion, breast, chest wall and regional lymph nodes in the same manner as described for Cases I and II.

Radiation therapy was well tolerated without systemic complaints. Dysphagia had its

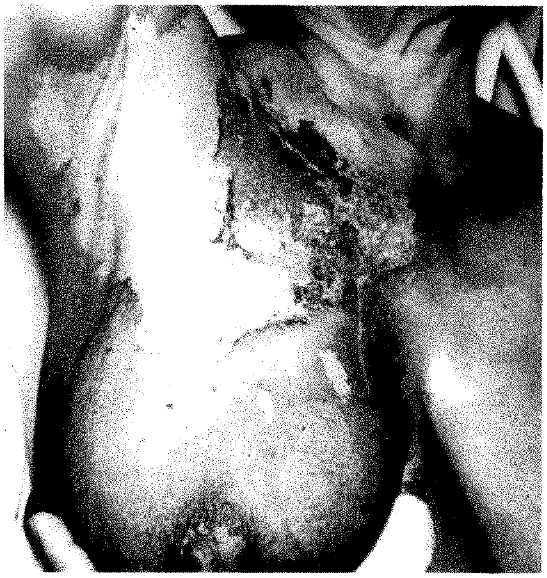

FIG. 2. Case III. Five weeks following completion of radiation therapy. Moderate desquamation of irradiated skin. Note good arm motion.

onset about 4 days following completion of therapy and disappeared in about 2 weeks. Erythema of the treated areas was noted at 12 days and progressed to a dry desquamation with a few small areas of moist reaction (Fig. 2). Healing was complete in 8 weeks. The tumor mass in the breast responded dramatically and was no longer palpable 2 weeks following completion of radiation therapy.

Limitation of motion of the right shoulder with fibrosis of the muscles at the anterior axillary line was noted in January, 1961, 5 months following treatment. At this time a chest roentgenogram showed some radiation fibrosis at the right pulmonary apex. A roentgenogram of the right shoulder in February, 1961 demonstrated no bone changes (Fig. 4).

Physiotherapy resulted in no real improvement of the shoulder symptoms. Increasing shoulder pain, respiratory stridor and hoarseness prompted a roentgenographic examination of the chest and shoulder in September, 1962, which again revealed some pulmonary fibrosis and, in addition, irregular destruction of the right humeral head (Fig. 5). The latter was interpreted as radionecrosis. Indirect laryngoscopy in October, 1962, disclosed paresis of the right vocal cord. Examination in November, 1962 showed marked telangiectasia and fibrosis of the chest wall and the patient could not abduct the right arm (Fig. 3).

A small 0.5 cm. lymph node was first noted to be present in the left axilla on February 14, 1963, and the following week numbness of the left lower extremity, weakness of the right lower extremity and a right Horner's syndrome became apparent. A sensory level at T10 to L1 on the left side was noted. The patient was placed on 5 mg. prednisone t.i.d. on March 27, 1963 and was last seen at the end of May, 1963, at which time her neurologic status appeared stable and no change in the size of the left axillary lymph node was detected.

DISCUSSION

Increasing knowledge of the dynamics of radiation effects on cells in tissue culture has raised questions concerning fractionation and distribution of dose in time.[4,8] The demonstration of complete recovery of sublethal damage before the first postradiation cellular division indicates the inefficiency of irradiating cells with an increasing number of fractions for the same over-all total dose. This is true when more than one "hit" is required to lethally damage a cell, which seems to be the situation in most cases. Apparently the number of fractions rather than the over-all time is

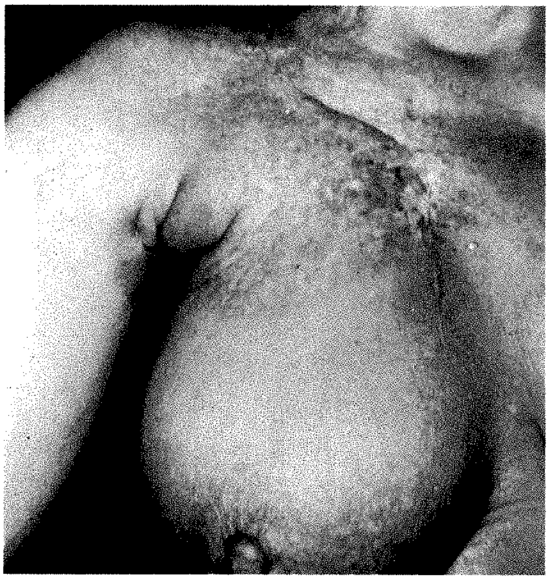

FIG. 3. Case III. Twenty-seven months after radiation therapy. There is marked telangiectasia and fibrosis of chest wall and pectoralis musculature. The arm cannot be abducted any further than noted in the photograph.

important in comparison of the biologic effects of different treatment regimens.

The tumor bed must also be taken into consideration in clinical radiation therapy. The relative recovery rate of normal tissue as compared to that of the tumor determines the ideal time-dose relationship. In the treatment of breast carcinoma, the tolerance to radiation of normal skin has been considered a limiting factor. Cohen,[2] in an analysis of the literature as well as observation of his own cases, concluded that the recovery factor for breast cancer (0.35) is similar to that for normal skin (0.33) and no advantage is obtained by prolonged fractionation as might be expected in the case of squamous cell epithelioma of the skin.

Friedman and Pearlman[5] estimated the average single fraction effective dose to be 2,200 r with a recovery factor of 0.25 in an analysis of a group of patients with skin metastases; Cohen's median curative single dose was estimated at 1,250 r.

Sambrook *et al.*[10] investigated the effect of several different treatment schedules on squamous cell carcinoma, basal cell tumors and adenocarcinoma of the breast. In breast carcinoma there was a definite superiority in a treatment schedule of 500 r twice a week over daily treatment to the same total dose over the same over-all time. A schedule of 1,000 r once a week for a total of 4,000 r produced a high incidence of necrosis, however.

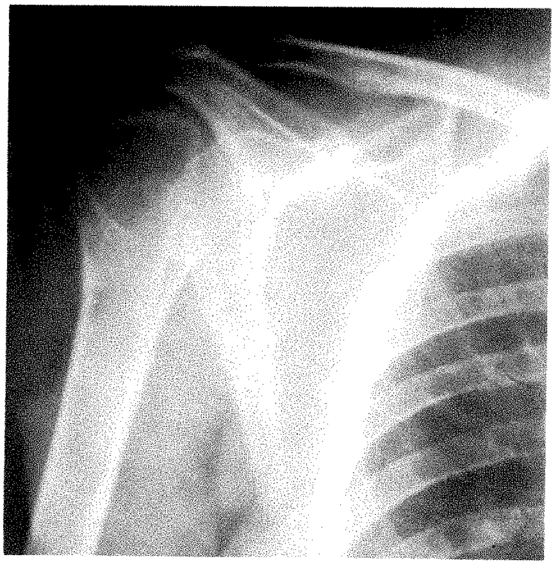

Fig. 4. Case III. Roentgenogram of right shoulder 6 months after radiation therapy is normal.

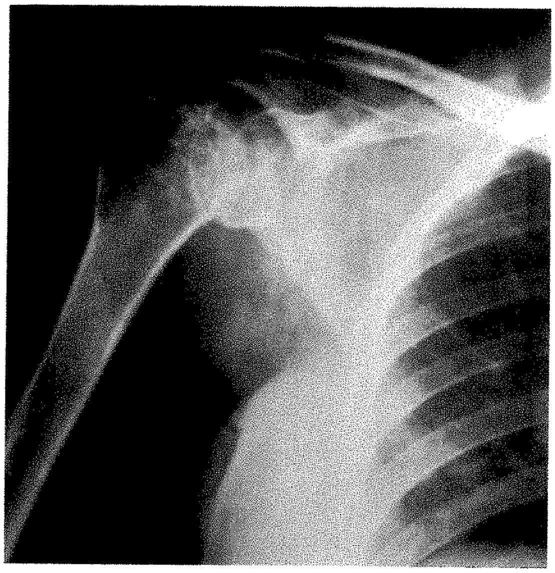

Fig. 5. Case III. Roentgenogram 25 months after radiation therapy shows mottled areas of increased density in the humeral head consistent with radionecrosis.

A group of patients with advanced breast cancer was treated by Cochran *et al.*[1] with a rapid, massive dose technique on the 22.5 mev. betatron. They delivered the total tumor dose in 2 consecutive days. Starting off with 1,250 r total tumor dose, this was later increased to 2,500 r. The immediate results were satisfactory but the late results have indicated complications similar to those experienced in this series.[9]

The treatment schedule used in the present report corresponds to the time-dose relationship as reported by Cohen for 7 days, but his figures are for daily treatment rather than two fractions. Tumor control appeared to be excellent and the radiation dose was well tolerated by the skin. In addition, there was minimal systemic reaction to these massive doses, probably associated with the relatively low integral dose and absence of side scatter with this high-energy radiation.

Unfortunately, the tolerance of underlying striated muscle was poor. Almost every patient so treated developed fibrosis and contracture, with ensuing restriction of shoulder joint motion. There was also a high incidence of dysphagia, secondary to esophagitis, but this was less distressing than the muscular fibrosis.

The 3 cases of radiation myelitis are, of course, an unfortunate complication. It is apparent that the central nervous system is unusually sensitive to this system of fractionation and extreme care must be used to exclude the spinal cord in treatment fields where rapid fractionation techniques are used.

Guttmann[6] reports that in 67 patients treated with radiation only for breast carcinoma with internal mammary lymph node and/or highest axillary lymph node involvement, 22 were free of disease after 5 years. In the present series, the follow-up is short and it is expected that most of the patients will ultimately develop metastases or local recurrence before 5 years have elapsed. In view of the high incidence of distressing complications in this series and the relatively good results obtained by Guttmann with more conventional technique, it was decided to discontinue the once a week treatment approach.

However, it is possible that some other type of treatment schedule rather than daily irradiation may be preferable in advanced breast cancer. Fewer treatments result in less expense and travel for the out-patient and may produce better tumor control. Also, more treatment time for more patients is allowed on overcrowded supervoltage equipment.

While the massive dose technique cannot be recommended where extensive volumes of tissue are to be included, there is still a place for this mode of therapy. In patients with advanced metastatic disease, this technique can be of value in treating the local breast tumor when this may be causing symptoms or threatening ulceration. The high complication rate is not to be expected when the pectoral muscles, esophagus and spinal cord are not included in the treatment fields.

SUMMARY

1. A series of patients with advanced breast cancer is presented that has been treated with an unconventional fractionation of the radiation dose, *i.e.*, 2,500 r maximum skin dose in two fractions over 7 elapsed days.

2. The degree of tumor control was excellent with control achieved in 9 of 12 patients in Stage III and partial control in 2 others. There was a poor response in only 1 patient.

3. In more advanced disease (Stage IV), complete control of local disease was achieved in 2 patients who survived for only a short time. Two other patients were partially controlled and 2 patients did not respond.

4. The high percentage of late fibrosis involving the pectoralis musculature and limiting motion about the shoulder joint, as well as of radiation myelitis caused discontinuance of the project despite excellent tumor response.

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THE INFLUENCE OF TIME-SPACING OF FRACT ON RESPONSE TO RADIATION*

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DETROIT, MICHIGAN

AN IMPORTANT advance in radiobiology was made by Elkind[3] when he demonstrated in tissue culture that cells sublethally damaged by radiation recover completely from this damage, so that the effect of a second dose is exactly the same as that for the first, provided the second dose is given after recovery is complete and before the onset of division after the radiation-induced delay. Then cell survival depends only on the number and size of the fractions. Applying these results to radiation therapy, he showed that curves of the same general shape as the time-dose curves developed from clinical data would result from calculation of the total dose required for iso-survival of cells for various numbers of treatments. In other words, time-dose curves could be explained, qualitatively at least, solely on the basis of the number of fractions into which the total dose is broken. With the usual daily treatment, longer over-all times would mean more and smaller treatments and would require a larger total dose; shorter over-all times would mean fewer and larger treatments and would require a smaller total dose.

There has been a tendency to extend these observations further than the data warrant and imply that time-dose curves can be explained quantitatively, as well as qualitatively, in these terms. But there are several aspects of clinical radiation therapy which do not conform to the limitations of the experiment in tissue culture. So-called "daily" treatment actually has gaps of 2 or 3 days at each week end. If conditions *in vivo* are the same as *in vitro* with respect to the time at which cell replacement begins—about 30 hours—one would expect some replacement during these gaps. Then time-dose curves w faster than predicted on the bas above reasoning because addition would be required to compensat replacement. Actually, just the seems to be true; time-dose curv ently rise more slowly than pre these calculation. Furthermore, t culture work extends only to 4 tr and perhaps cannot be extrapolat large number—approximately 30 used clinically. We do not know dose-response would remain the this many repetitions, that abili cover would be undamaged, or replacement would not be delayed take place more slowly. Finall separated cells of uniform radios were used in the tissue culture ex while *in vivo* we deal with a mixtu of varying degrees of oxygena sensitivity in close contact with e so that interaction among them is All these differences might well m simple process seen in tissue cultu

EXPERIMENTAL INVESTIGAT

Some of these differences wer gated in the present experiment. portance of intervals long enoug replacement to take place, the ti treatment series at which such int cur, and the influence of their le examined in spontaneous tumor using 12 treatment sessions.

It has already been shown in experiment[2] that if the weekly d constant, fewer and larger fracti though the intervals between longer, result in a higher cure ra these conditions the number and

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* From the Department of Radiology, Henry Ford Hospital, Detroit, Michigan.
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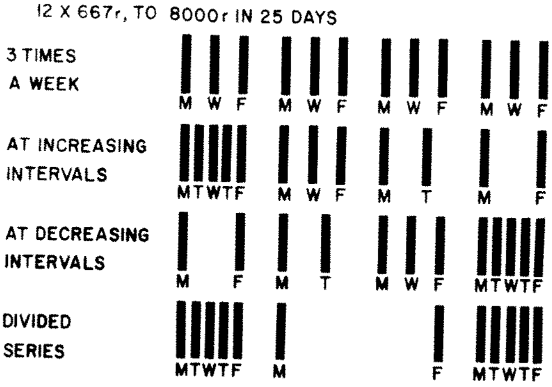

Fig. 1. Schematic representation of the treatment plans which were compared.

fractions are more important in the determination of cure rate than the cell replacement taking place during the intervals between fractions. In the present experiment the number and size of the fractions were kept constant at 12×667 r but the weekly dose varied as the intervals between them changed in length and position in the treatment series.

A total of 333 C3H/HeJ mice bearing spontaneous mammary adenocarcinomas between 8 and 19 mm. in diameter was used. These mice have been employed in several earlier experiments; all details of their handling and of the radiation technique were reported then[2] and will not be repeated here. To make certain that the fractionations examined included intervals long enough for cell replacement to take place, treatment every day without any gap at the week end (over-all time 11 days) was compared with treatment three times a week (over-all time 25 days). Cure rates were 24 per cent and 19 per cent, respectively, for all mice beginning treatment. If the number and size of the treatment doses were the only determining factor in dose-response, results would have been the same. The difference represents cell replacement during the longer intervals in the second treatment plan. It is recognized that cell replacement may not be the only factor which influences cure rate here, but for the sake of simplicity it is the only one mentioned at this point.

To find the importance of the length and position in the treatment series of such intervals, 4 treatment plans were compared, all involving 12×667 r to 8,000 r in 25 days. They are shown schematically in Figure 1 and consisted of treatment (1) three times a week, (2) at increasing intervals, (3) at decreasing intervals, and (4) in a divided series. The longest interval in the first plan was 3 days (over the week end), in the second and third plans 4 days, and in the last 11 days. Comparison of their results should show the influence of the length of the interval. Plans 2 and 3 were the same except that in one the long gaps occurred near the end of the series and in the other near the beginning. Differences here should show the influence of the position at which the gap occurs in the treatment series. (Another reason for including Plan 4 is the success of "split-course" therapy of human tumors, as reported by Sambrook[5] and Scanlon[6].)

Response to treatment was evaluated by the fraction of tumors controlled. This was determined by palpation, only those tumors being classed as controlled which showed no sign of recurrence to the death of the mouse. Palpation gives a much more accurate estimate of cure in mice than in humans. Mouse skin is free enough so that it and the tumor immediately underlying it can be picked up between the thumb and forefinger. Tumors only 1 mm. in diameter can be easily detected under these conditions. Mice were examined weekly until their death and their status at last examination was used for classification. Follow-up ranged from a few days to more than 200, with a mean time of 85 days for all mice, or 96 days for cured mice and 83 days for mice dying with tumor present.

Results of treatment among mice completing the series are presented in Figure 2. They show that the 3 times a week plan with the shortest maximum interval of 3 days gives the best result. Any plan with intervals longer than this gives poorer results. Long gaps do more harm to the cure rate when they occur near the beginning

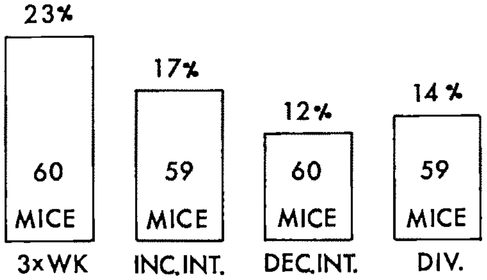

FIG. 2. Control of treated tumor among those mice completing treatment.

than when they occur near the end of a series, that is, the cure rate is better for increasing intervals (Plan 2) than for decreasing intervals (Plan 3). But if a sufficiently large dose is given early in the series, even a longer gap between treatments later on (Plan 4) will not decrease the cure rate as much as when the gaps occur early (Plan 3).

The differences shown here are not statistically significant. Real, but small, differences require a very large number of test objects for statistical significance. Over 6,000 mice would be required to make all these differences significant at the 5 per cent level. The present study was the work of a year and a half, so it is obviously not practical to attempt this, especially since, as will be seen later, only small differences would be expected.

DISCUSSION

Let us first consider the difference in results between Plans 2 and 3, increasing intervals and decreasing intervals. They show that a long treatment interval harms cure rates more when it occurs near the beginning of the series than when it occurs near the end. Near the beginning of the series more cells are present than near the end, when lethally damaged cells have disappeared. If more cells divide during the period between treatments, the increase in absolute number of cells is greater. Essentially, then, we are treating a larger total number of cells if we permit division near the beginning of the series. Since the end result of treatment is survival of a certain fraction of the cells, the absolute number in this fraction will be greater and the cure rate will be lower.

Furthermore, cells surviving irradiation grow more slowly,[4] so that replacement will be less late in the series and gaps at this time will not be as important to the cure rate. It is possible that greater delay in resumption of division may result from repeated irradiation and also affect cure rate. Dose-response may be less near the end of the series since a greater proportion of anoxic cells may remain after the more radiosensitive oxygenated cells have been largely eliminated.

Now let us consider the 3 plans which include an early, large dose. Plans 1, 2, and 4, treatment 3 times a week, at increasing intervals, and the divided series, all included 6×667 r, or 4,000 r, during the first 2 weeks of the series. The longest intervals between treatments were 3, 4, and 11 days, respectively. Cure rate dropped from 23 to 17 per cent as the 3 day interval was increased to 4, but only to 14 per cent as the 4 days became 11. Evidently, cure rates decrease at the interval increases, but not in proportion to its length.

The explanation for this may be found in Figure 3. This shows the number of cells in mitosis before, and at different times after, a dose of 667 r, expressed as per cent of the preradiation level. The difference between 1 and 2 days was very slight. After this the number of cells in mitosis increased more and more rapidly and appeared to return to the preradiation level at about 4 days, after which it would remain the same.

In changing from treatment every day to treatment 3 times a week, intervals of 2 days were inserted but these had little more effect than the 1 day intervals. The 3 weekends introduced intervals of 3 days and these did more to lower the cure rate. Treatment at increasing intervals had several intervals of 3 and 4 days during which replacement was appreciable and cure rates dropped still more markedly. But the last plan, the divided series with the 11 day interval occurring after a steady rate of division had been reached, was little worse than the 4 day interval.

Up to 4 days the effect of increasing the interval between treatments depends on the speed with which the preradiation mitotic rate is regained or the speed with which the sublethally damaged cells repair their damage. This would depend, for one thing, on the size of each fraction.[2] After 4 days (for this dose) the effect of further increase in the interval is related to the rate of growth, or doubling time, of the tumor and is proportional to the length of the interval minus 4 days.

Incidentally, this curve illustrates another difference between cells in tissue culture and tumors *in vivo*. In the tissue culture the cells are in phase, irradiation arrests mitosis and a plateau occurs during which there is no division. In these tumors *in vivo*, as can be seen from Figure 3, there are some cells in mitosis at all times after irradiation and no such plateau occurs.

In order to find the doubling time for this mouse tumor, untreated tumors were measured daily by fitting them to holes in stiff paper. Although the rate was not the same among the different mice, nor at different times in the same mouse, the mean doubling time in the range of tumor size used in this experiment was about 8 days. Actually, during the 11 day interval in the middle of the treatment series, it would be somewhat longer than this, as already mentioned. Human tumors, in general, have a very much longer doubling time than this[1] and a gap of 11 days should result in less cell replacement and hence less decrease in cure rate than was found here. Very little increase in dose would be required to compensate for it. This would explain the good results reported by the radiotherapists using "split-course" therapy.

The time to return to a normal, preradiation mitotic rate, on the other hand, depends on the size of the dose of radiation and might be more rapid for the smaller doses used in radiation therapy. If this is the case, a relatively greater drop in clinical cure rate would be expected than was found in the mice if short intervals, but greater than 1 day, occurred between treatments.

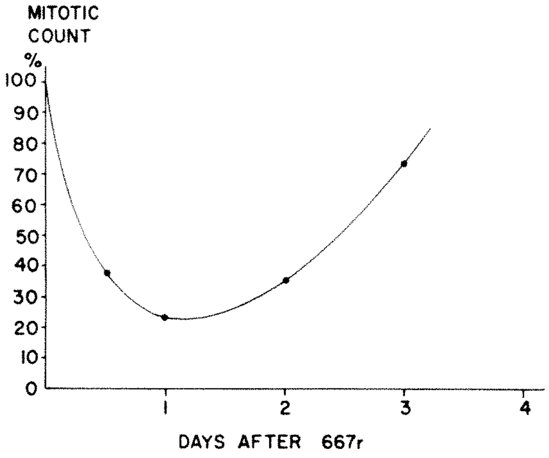

Fig. 3. Number of cells in mitosis before, and at various times after, irradiation with 667 r, expressed as per cent of the preradiation level in C3H mammary adenocarcinomas. (This study was done by Dr. John W. Budd, pathologist at Hollywood-Presbyterian Hospital, Los Angeles, California.)

SUMMARY

Spontaneous mammary adenocarcinomas in C3H mice were irradiated with 12×667 r to 8,000 r in 25 days with different spacings of the treatments within this time period. Results showed that gaps between treatments which occur early in the treatment series will harm cure rates more than if they occur late in the series and that the decrease in cure rate increases, although not proportionally, with length of the gap.

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The author would like to express appreciation for the technical assistance of Mr. Athan Carros in treating the mice.

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CARCINOMA OF LUNG: RESULTS OF RADIOLOGICAL TREATMENT*

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THIS paper is based upon an analysis of 225 patients treated during the years 1953 to 1956, inclusively, for carcinoma of the lung. During that time 921 such cases were recorded in Memorial and James Ewing Hospitals. Of these, 632 were not suitable for inclusion in this report for the reasons shown in Table I. Fifty-three patients are not reported because, although they had radiation therapy, the records are incomplete or are missing. Finally, 11 other patients are technically eligible for the study, but the hospital records were not available and must be presumed to be missing. Thus, of the 921 patients, 696 were not eligible for this study.

It should be stated here that the conclusions which will arise from this review do not change in any marked fashion the well-established opinion in the literature that the treatment of far-advanced carcinoma of the lung, which is the radiologist's normal lot in attempting to help patients with this disease, is a discouraging task.

The 225 eligible and available cases were reviewed and even patients who received only 2 or 3 treatments were included when they satisfied the conditions described above.

STAGING

In a prior paper on this subject[1] a method of staging for carcinoma of the lung was presented. This staging has been modified (Table II) so that it now is based primarily on anatomic and clinical considerations.

As a guiding principle, any information acquired from the diagnostic work-up may be used in staging. Any information obtained from a therapeutically oriented procedure may not affect staging.

Table I

CARCINOMA OF THE LUNG

(Memorial and James Ewing Hospitals)

Total number of cases registered:	
1953—229	
1954—254	
1955—205	
1956—233	
	921
Cases not included because:	
Lung was partially or wholly resected	632
Primary lesion was not treated at Memorial Hospital	
Had only radon seed implantation	
Had only chemotherapy	
Had only supportive treatment, or no treatment	
Slides were not reviewed at Memorial Hospital	
No pathology report is in the chart, or diagnosis is doubtful	
Had radiation therapy, but records are incomplete	53
Hospital charts are not available	11
Not included	696
Included	225
Total	921

FACTORS OF TREATMENT

The patients were treated by a 1 mev. roentgen-ray machine, a telecobalt 60 unit, or by 250 kv. roentgen-ray units. The Mark 1 IAEC cobalt 60 teletherapy unit was used at either 70 or 95 cm. source skin distance; the 1 mev. unit was used either at 70 or 100 cm. target skin distance, commonly the former; and the G.E. 250 kv. unit was used with a half value layer of 2.0 mm. of copper at 70 cm. target skin distance.

Field sizes were determined from data

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* From the Department of Radiation Therapy, Memorial Hospital for Cancer and Allied Diseases, and James Ewing Hospital, New York, New York. Presented in part at the Tenth International Congress of Radiology, Montreal, Canada, August 26-September 1, 1962.

obtained on physical and roentgen examinations. In general, the primary lesion and the regional lymph nodes were treated with margins of at least 2 cm. in excess of those necessary for the volume believed to contain the cancer. Tissue doses with supervoltage therapy ranged from less than 500 rads in 5 days to 6,800 rads in 58 days. Commonly, the treatment schedule called for a 200 rad midplane dose daily. The usual weekly increment was 1,000 rads.

One-hundred and seventy-four patients were treated with supervoltage radiation; 51 were treated with 250 kv. units. Randomization was not used for the assignment of the patients to the various units.

Table III shows the distribution of patients according to age, sex, histology and staging. The age and sex distribution in this series was a typical one for this disease. The category "anaplastic carcinoma" comprises only cases reported by the histologist as anaplastic or "oat cell type;" 22 were of the "oat cell type." The "undetermined" category contains cases reported as "carcinoma" without further qualification.

The distribution by staging is as would be expected in an institution in which patients deemed to have possibly resectable lesions are treated with an operative procedure. Of the 225 cases, 140 were clinically classified as inoperable and nonresectable (Stage IV). It is obvious, therefore, that the bulk of the data to be reported and discussed in this paper is derived from experience with patients with far advanced cancer. For example, in 10 patients, treatment of metastases preceded treatment to the primary lesion, ranging in time from a few weeks to 7½ months. In several other cases, radiation therapy was given concurrently to the primary lesion and to a metastatic area.

TABLE II

STAGING OF CARCINOMA OF THE LUNG

Stage I. Operable and Resectable Cases
1. Discrete tumor, roentgenologically not adjacent to the chest wall or merging with hilar shadow
2. No suggestion of mediastinal lymphadenopathy
3. Distinct atelectasis of a lobe or small segment

Stage II. Operable and Probably Resectable Cases
1. Discrete tumor, roentgenologically adjacent to the chest wall or merging with hilar density or associated with an enlarged hilus
2. Mediastinal lymphadenopathy by roentgenography or bronchoscopy
3. A main stem lesion more than 1 cm. from carina
4. Chest wall invasion adjacent to the tumor
5. Involvement of rib (not metastatic)

Stage III. Operable but Probably Not Resectable Cases
1. Any case of oat-cell or anaplastic carcinoma
2. Involvement of esophagus
3. Involvement of vertebral body
4. Horner's syndrome
5. An elevated venous pressure over 150 mm. H_2O in arm on affected side
6. Main stem bronchus involved within 1 cm. of carina
7. Pleural effusion negative for cancer cells or not studied
8. Either phrenic or recurrent laryngeal nerve paralysis

Stage IV. Nonoperable and Nonresectable Cases
1. Extrathoracic metastases
2. Metastases to opposite lung
3. Pleural effusion with proved cancer cells
4. Both phrenic and recurrent laryngeal nerve paralysis
5. Any combination of conditions in Class III

Table III

CARCINOMA OF THE LUNG

DISTRIBUTION ACCORDING TO AGE, SEX, HISTOLOGY AND STAGING

Age	Male	Female	Undetermined	Epidermoid	Anaplastic	Adenocarcinoma	Terminal	Stage			
								I	II	III	IV
31–40	4		1	3						2	2
41–50	31	7	7	17	7	4	3	1	1	6	30
51–60	68	7	10	41	14	5	5		16	12	47
61–70	78	4	6	55	13	7	1		12	21	49
71–80	24	2	5	19	1		1	1	8	5	12
	205	20	29	135	35	16	10	2	37	46	140
	225		225					225			

FOLLOW-UP

For the Service patients, follow-up was the joint responsibility of the Thoracic Service, Department of Surgery and the Thoracic Clinic of the Department of Radiation Therapy. For semiprivate and private patients, the attending physician for the patient commonly discharged this responsibility. In instances where the patients lived at great distances from Memorial Hospital, follow-up was primarily by letter from the referring physician.

RESULTS

The results of treatment are reported by Stages. Figure I shows the experience for Stage II carcinoma. In this and in subsequent Figures, the patients are divided first into those who had surgery, then this category is subdivided into those patients who had implants at operation and those who had thoracotomy only. The second major group is composed of those who had no exploratory thoracotomy. Further, the modality of treatment is considered, those treated with 1 mev. or cobalt 60 being in the upper portion of the groupings mentioned above. Each case is assigned a position in descending order according to the maximal midplane tissue dosage delivered. On each lifeline, the arrow pointing upward indicates the time of thoracotomy, if any. The pathology is indicated by the character of the lifeline for each patient.

Thirty-seven patients were classified as Stage II. The average time of survival for this group was 9.8 months and the mean survival time 8.8 months. Twenty-five patients lived more than 6 months, 12 lived more than 12 months, and 7 more than 18 months. One patient (Case 205) is not included in this table. He was a 51 year old male presenting complaints of chest pain, cough and hemoptysis. In June, 1948 this patient underwent right thoracotomy elsewhere for a large mass occupying the right upper lobe. The tumor was found to be fixed to the surrounding structures and was considered nonresectable. After surgery, he received a course of radiation therapy for 45 days. The dosage and factors are unknown. In February, 1956, he again developed hemoptysis and was explored at Memorial Hospital. The lesion was considered nonresectable. Frozen sections were reported as anaplastic carcinoma. Postoperatively, he received a course of nitrogen mustard (HN_2) intravenously and 3,100 rads to the right hemithorax through 23×13 cm. anterior and posterior ports with the 1 mev. unit. There was relief of hemoptysis for several months. Roentgenograms taken 1½ months after completion of treatment showed regression. In September, 1957 because of progression of the disease he was again irradiated, 1,200 rads being

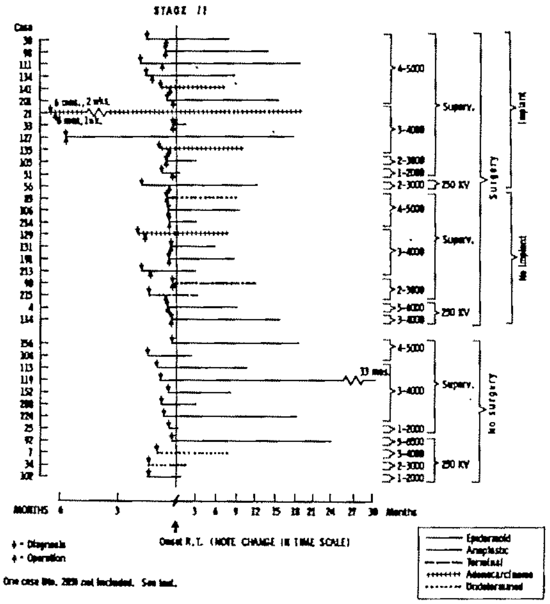


FIG. 1. Carcinoma of the lung, Stage II. Duration of life after start of external beam irradiation. (See text for explanation of figure.)

delivered. The patient expired in March, 1958, 9 years and 8 months after the first thoracotomy. No autopsy was performed. Since the histologic diagnosis of cancer of the lung was made at the second thoracotomy and since the history as a whole was so atypical, we have felt it wiser to exclude this patient from tabular presentation.

Stage III lesions are shown in Figure 2. The manner of reporting is similar to that described for Stage II. In this group there were 46 patients. Twenty-two patients lived more than 6 months, 9 survived more than 12 months, and 7 survived 18 or more months. The longest survival time was 52 months. The average time of survival for all patients was 8.7 months, the mean survival time 5.3 months after the beginning of radiation therapy. One patient (Case 199) is not included. He was a 67 year old male who had an epidermoid carcinoma of the left lung. After receiving 300 rads at Memorial Hospital, subsequent treatment was given elsewhere. No information could be obtained regarding the total dose delivered. He survived 20 months after the start of irradiation.

The results for 140 patients in Stage IV are shown in Figures 3, *A*, *B* and *C*. Sixty-six patients survived 6 or more months, 24 survived 12 months or more, and 5 survived 18 months or more. The longest survival time was 29.5 months. The average time of survival was 6.5 months, the mean survival time 5.1 months.

Twenty-five patients had radioactive implantation at the time of exploratory thoracotomy. They are shown in Figure 4. The number of millicuries of radon or the milligrams of radium equivalent for iridium 192 is given at the left of the table. Unfortunately, data regarding the volume of the implant are not available for most of these patients; therefore, no basis exists for the estimation of tissue dosage. Volume dosage estimations are routinely

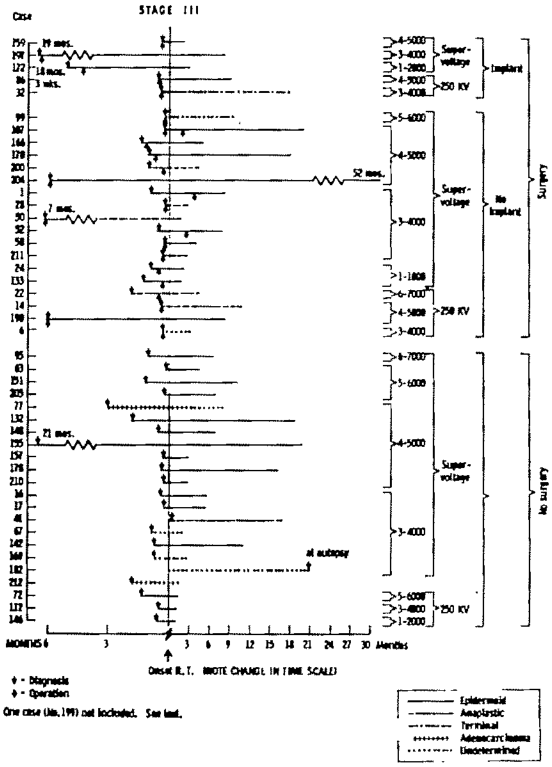


FIG. 2. Carcinoma of the lung, Stage III. Duration of life after start of external beam irradiation. (See text for explanation of figure.)

available for patients treated after 1957. In Stage II, 13 patients were implanted; in Stage III, 5; and in Stage IV, 7. Survival, histology, dose, and modality of radiation therapy are given in the manner cited above. As in the earlier figures, the survival time is calculated from the start of external irradiation. For an estimation of the time of survival after implantation, the length of the lifelines between operation and the beginning of radiation therapy must be added. The table shows that in some of these patients, external radiation was given many months after implantation, commonly because of evidence of regrowth of the primary lesion. These patients, therefore, must be considered separately from those in whom the implantation was supplemented promptly by external irradiation.

CHEMOTHERAPY

In the entire series of 225 cases, 55 patients received nitrogen mustard during the course of their disease. Forty-four of

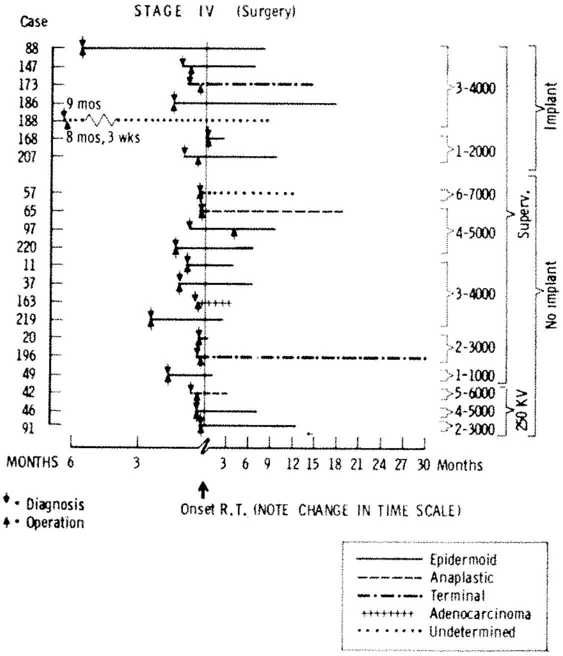


Fig. 3. (*A*) Carcinoma of the lung, Stage IV. Duration of life after start of external beam irradiation in patients who also had a surgical procedure.

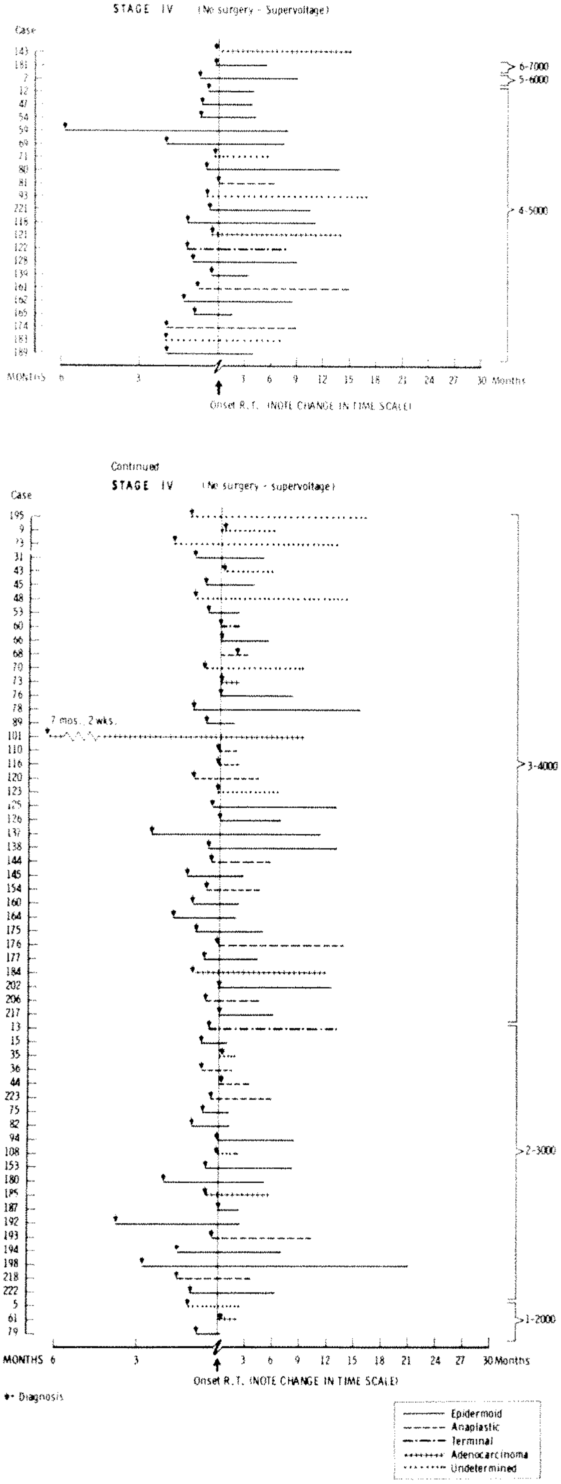


Fig. 3. (*B*) Carcinoma of the lung, Stage IV. Duration of life after start of supervoltage irradiation in patients who did not have surgery.

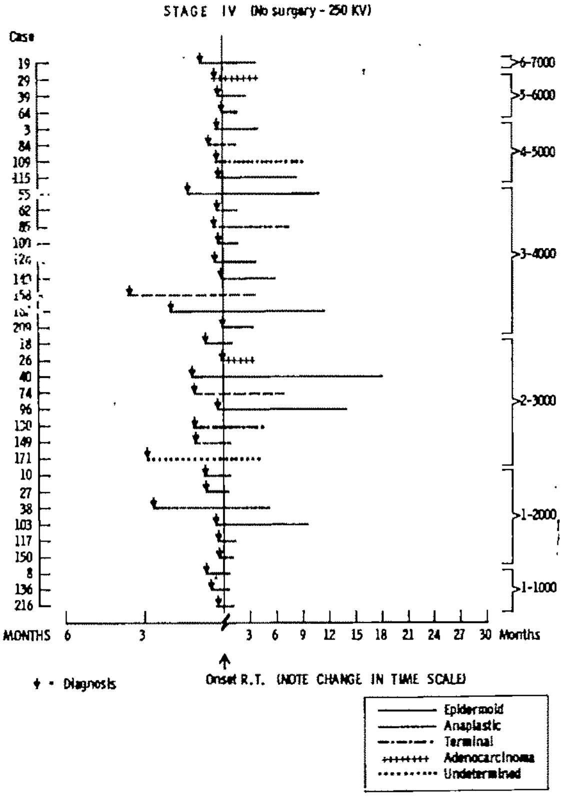


FIG. 3. (*C*) Carcinoma of the lung, Stage IV. Duration of life after start of 250 kv. irradiation in patients who did not have surgery.

these were classified as Stage IV carcinoma. In 33 patients nitrogen mustard was given before external radiation therapy. It is not possible to evaluate the impact of the nitrogen mustard upon the survival time of these patients. Of these patients, 27 were classed as in Stage IV. Their average survival time was 4.6 months, as compared with an average survival time for the entire group of Stage IV patients of 6.5 months. It is reasonable to assume that the patients receiving nitrogen mustard had on the whole more advanced disease than those not receiving the agent, and, therefore, conclusions pertaining to the shorter period of survival cannot be made.

The relationships of survival time by stage of disease, by dose delivered, by the quality of radiation and by the use of implants are presented in Figures 5, 6 and 7. (One patient, Case 87, is not included. He was a 66 year old male, Stage IV, who received 4,100 rads tissue dose for an epidermoid carcinoma of the lung. No follow-up data were available.) No obvious correlation is shown between dose or quality of radiation and length of survival or between survival time and histology or staging in this group of patients; however, regarding histology, for cases other than epidermoid carcinoma, the number of patients was relatively small and correlation could not be expected. In the epidermoid carcinoma patients, the average survival time was 10.3 months in Stage II, 9.3 months in Stage III, and 6.2 months in Stage IV.

For Stage II, of the 7 patients who survived more than 18 months, 6 had a diagnosis of epidermoid carcinoma and 1 a diagnosis of adenocarcinoma. For Stage III, of the 7 patients who survived 18 or more months, 1 patient had a diagnosis of terminal bronchiolar carcinoma, 1 a diag-

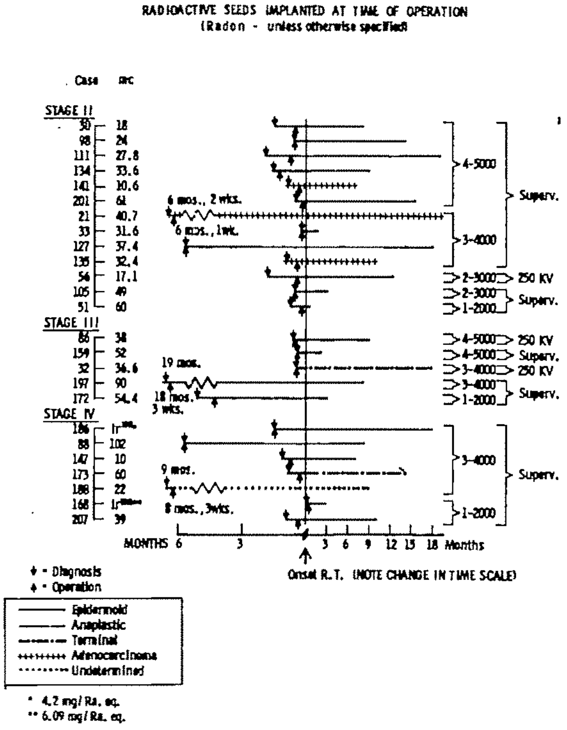


FIG. 4. Carcinoma of the lung, Stage II, III and IV. Radioactive seed implantation at the time of operation.

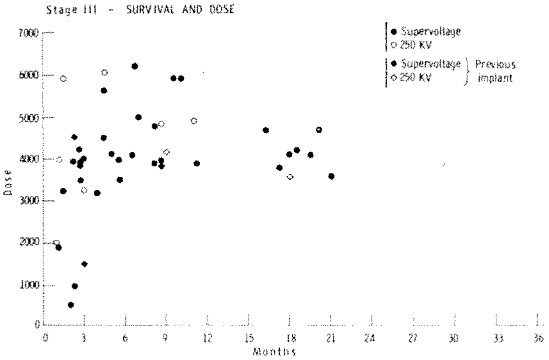
nosis of undetermined carcinoma, and 5 a diagnosis of epidermoid carcinoma. In Stage IV, of the 5 patients who lived more than 18 months, 1 had a diagnosis of a terminal bronchiolar carcinoma, 1 of anaplastic carcinoma, and 3 of epidermoid carcinoma.

The mean survival time as a function of staging, and as a function of the presence or absence of thoracotomy, and/or implantation is shown in Table IV. The number of patients in all categories, save Stage IV (no surgery), is so small as to make any significance doubtful. For the patients who had implantations, the mean survival time is given from the time of the procedure and also from the beginning of radiation therapy.

DISCUSSION

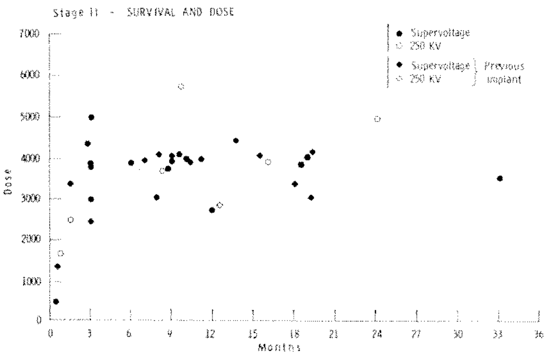
The present study supports the conclusions reached in our prior work.[1]

For those patients with clinically operable Stage I or II carcinoma, the departmental experience proved of interest. In general, these are patients for whom an operation was urged but was refused. In Stage I, 2 patients were treated. One patient (Case 179) had an epidermoid carcinoma and lived for 4 years after treatment. He was a 71 year old male with a past history of cholecystectomy for cholelithiasis, a chronic gastric ulcer, malnutrition and episodes of painful swelling of both ankles. In February, 1956 he complained of tenderness in the left breast with evidence of gynecomastia and pain in the shoulders and ankles. A chest roentgenogram taken in October, 1956 revealed a mass in the left upper lung field, measuring about 1×3 cm. in diameter. Sputum studies were negative. He had a minimal amount of cough and no chest pain. An exploratory thoracotomy was advised, but was refused. From November 27, 1956 to January 3, 1957, following a clinical diagnosis of carcinoma of the lung, the left lung lesion received a tissue dose of 4,300 rads with the 1 mev. machine through opposing 9×13 cm. anterior and posterior ports. Subsequent roentgenograms of the chest revealed no progress of the pulmonary lesion for a period of over 3½ years. He was



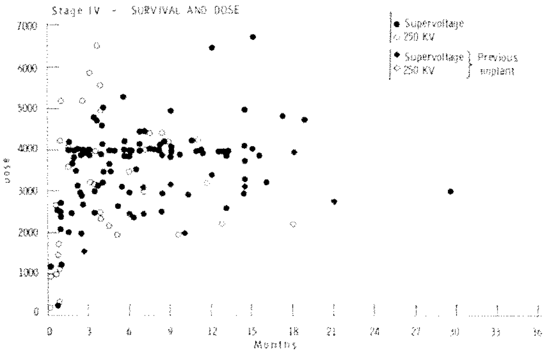
One case (No. 199) not included. See text.
Survival since onset of external R.T. even for implanted cases.

FIG. 6. Carcinoma of the lung. Correlation of survival and radiation dose in Stage III.



One case (No. 205) not included. See text.
Survival since onset of external R.T. even for implanted cases.

FIG. 5. Carcinoma of the lung. Correlation of survival and radiation dose in Stage II.



One case not included (No. 87). See text.
Survival since onset of external R.T. even for implanted cases.

FIG. 7. Carcinoma of the lung. Correlation of survival and radiation dose in Stage IV.

asymptomatic during this time and then began to complain of pain in the left scapula. In March, 1960 the sputum became positive for epidermoid cancer cells. In April, 1960 he received another course of irradiation to the left upper lung, 3,000 rads tissue dose being delivered in 24 days by the Co^{60} unit. The patient had multiple complaints thereafter, and expired on December 6, 1960. No autopsy was obtained.

The other patient, Case 225, was a 45 year old male whose tumor was classified histologically as undetermined carcinoma. He was living at the time of the preparation of this paper, 5 years and 5 months after the beginning of treatment. He received 28 mg. of HN$_2$ intravenously. Four days later treatment was started with the 1 mev. machine through opposing 14×14 cm. anterior and posterior ports, a tissue dose of 3,000 rads being given in 17 days. The histologic slides from this patient were reviewed recently by the head of the Cytology Service of the Department of Pathology and the diagnosis of carcinoma was confirmed.

Three patients in Stage II refused surgery and were treated by radiation only. Case 119 was a 71 year old male with a right upper lobe lesion in the proximity of the hilar region, measuring 5×6 cm. in diameter. The chief complaints were progressive dyspnea and a productive cough of 1 year's duration. Sputum cytology was reported as positive for malignant cells, Class V epidermoid carcinoma. From July 10, 1955 he was treated with 250 kv. rotation technique through a 9×11 cm. port. A tissue dose of 3,600 rads was given to the lesion in the right lung. There was favorable symptomatic and objective response lasting 20 months. In March, 1957 roentgenograms of the chest showed an increase in the size of the lesion. Cough was the only complaint. The right hilus was irradiated with the 1 mev. machine, a tissue dose of 3,000 rads being delivered through 9×12 cm. anterior and posterior ports. The patient was asymptomatic for 7 months. He then developed bone metastases and expired April 2, 1958, 33 months after radiation therapy was instituted.

Case 224 was a 70 year old male referred to Memorial Hospital on October 14, 1956, after bronchoscopy elsewhere revealed an obstructive neoplastic mass in the right intermediate bronchus, about 2 cm. distal to the upper lobe orifice. Review of the histologic slides indicated epidermoid carcinoma. From October 15 to November 14,

Table IV

CARCINOMA OF THE LUNG
SURVIVAL TIME CORRELATED WITH STAGING

		No. of cases	Mean survival (mo.)		
Stage II	Thoracotomy and implant	13	(10.3)*	10.2†	8.8
	Thoracotomy	11		8.4	
	No surgery	12		8.3	
Stage III	Thoracotomy and implant	5	(9.2)*	8.3†	5.3
	Thoracotomy	18		4.5	
	No surgery	22		5.5	
Stage IV	Thoracotomy and implant	7	(13.7)*	8.6†	5.1
	Thoracotomy	14		6.5	
	No surgery	118		4.7	

* Since time of implant.
† Since time of radiation therapy.

1956, the right lung lesion was treated through opposing 13×13 cm. anterior and posterior fields with the 1 mev. unit. The tissue dose was 4,000 rads. There was objective as well as symptomatic improvement for several months after treatment. The patient was followed elsewhere and died on April 28, 1958, 18½ months after beginning of treatment.

Case 208, a 67 year old male, was referred to Memorial Hospital after the diagnosis was established at Kings County Hospital. Chest roentgenograms revealed a mass measuring about 8 cm. in diameter in the posterior apical segment of the right upper lobe. A right scalene lymph node biopsy was reported negative. Cytologic examinations of the sputum were reported positive for malignant cells, Class v epidermoid carcinoma. He refused thoracotomy and was given radiation therapy to the right lung lesion. From February 4, 1957 to March 7, 1957 he received 3,900 rads tissue dose through 22×10 cm. anterior and posterior ports with the 1 mev. machine. A chest roentgenogram taken 1 month later showed decrease in the size of the lesion. A slight pleural effusion was present in the right base. There was no improvement of his cough. Two months after completion of radiation therapy, he was re-admitted as an emergency patient because of marked dehydration, weakness and back pain. A skeletal survey failed to demonstrate any metastases. He had a downhill course and expired a few days later on May 4, 1957. No autopsy was done.

Also of interest are those patients explored after completion of irradiation. In Stage III, 3 and in Stage IV, 2 patients were given radiation therapy and subsequently were operated upon. For these patients the tissue doses ranged from 1,500 rads to 4,700 rads at approximately the rate of 1,000 rads per week. The time of surgery varied from 10 to 120 days after beginning of the irradiation. One case in Stage III was explored and deemed unresectable by virtue of a large bulky tumor and enlarged hilar lymph nodes adherent to the diaphragm. Postoperatively he received 4,600 rads in 36 days and was subsequently re-explored. There was marked regression of the primary tumor. The hilar lymph nodes, however, had only slightly decreased in volume. A resection could not be done. This patient survived 20 months after institution of radiation therapy.

Another of the Stage III patients who was explored after irradiation has been previously described (Case 199). The remaining patient survived 8 months after therapy. The 2 patients in Stage IV survived an average of 6 months after radiation treatment. The pulmonary lesions could not be resected in any of these 5 patients.

Correlation of symptomatic and objective response was attempted. Of the 225 cases, 39 were not suitable for either symptomatic or objective evaluation. Thus, only longevity was available for appraisal of those patients. Of the remaining 186 cases with available information, 113 showed evidence of symptomatic relief. It is of interest to note that in this group, only 59 showed evidence of favorable objective response.

SUMMARY AND CONCLUSIONS

An analysis of 225 cases of carcinoma of the lung is presented. These patients were treated in the Department of Radiation Therapy of the Memorial and James Ewing Hospitals. A modification of the previously reported staging for this disease is suggested. Using this method of staging, the majority of the patients treated were placed in Stage IV. Survival of these patients is so short that doubt exists that radiation therapy added to their life span. Using longevity as the criterion of evaluation, it is believed that the Stage I and II cases with carcinoma of the lung were benefited by radiation therapy; however, the number of patients in the reported series is so small that no proof can be offered for this opinion. The evidence suggests that with radiation treatment symptoms associated with this disease can be relieved or may completely disappear in the majority of patients.

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We wish to express our gratitude to Dr. W. W. Watson, Chief of the Thoracic Service, Department of Surgery, for his cooperation in the preparation of this paper and to acknowledge the advice and assistance of Dr. E. Cliffton in revising the staging criteria for that proposed here.

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Vol. 91, No. 1

THYMOMAS—ROENTGEN CONSIDERATIONS*

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NEW YORK, NEW YORK

ALTHOUGH the thymus has been regarded as important since ancient times (*i.e.*, as the seat of courage by the early Greeks), the actual functions of the thymus gland are only now beginning to be unraveled.[4] So, too, have tumors of the thymus gland been poorly understood and only recently have emerged as clearly defined pathologic lesions.[2,5,17] In this report we are reviewing the roentgenologic features in a series of 65 thymomas observed at the Columbia-Presbyterian Medical Center during the years 1942 to 1961. Most of these tumors have occurred in patients with myasthenia gravis.

Thymomas, though quite rare, are the most common surgical tumors of the anterior mediastinum. Most typically these tumors protrude from the anterior mediastinum at the base of the heart (Fig. 1, *A* and *B*). Exceptionally, they have arisen from thymic rests in the neck, in the lung and in the subpleural tissue of the chest wall. Although the great majority of the tumors are encapsulated, they are often adherent to adjacent structures. About 25 per cent are locally invasive and some spread by local implantation on pleural surfaces. Distant metastases are very rare[5,8,17,19] and are usually to the liver.

Not considered in this study are certain other tumors of the anterior mediastinum which may involve the thymus such as thymolipoma; cysts of developmental, lymphatic or hassallian origin; hyperplastic mediastinal lymph nodes; teratomas and metastatic carcinomas. Some undifferentiated carcinomas of the anterior mediastinum may be of thymic origin although they are not usually regarded as thymomas.

In thymomas, the two major thymic cell types, the epithelial cells of endodermal

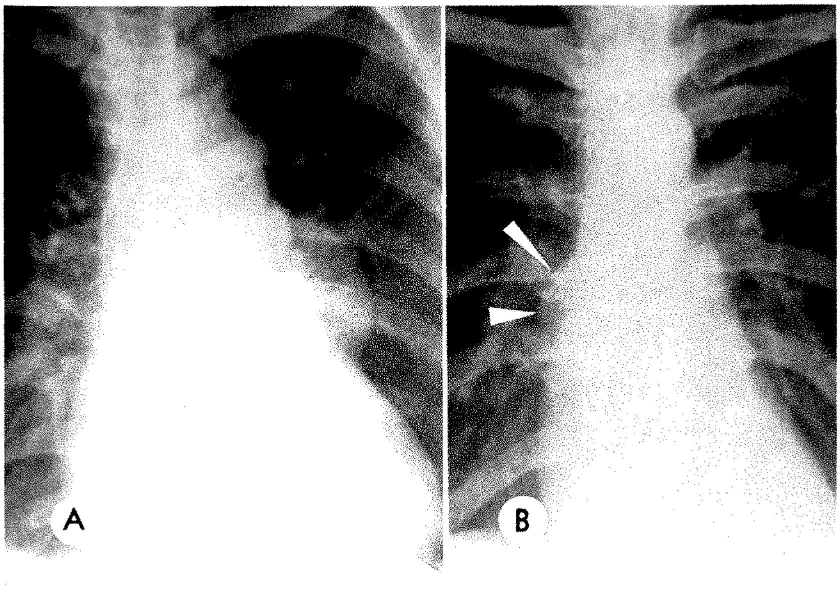

Fig. 1. (*A*) Thymoma presenting as asymptomatic anterior mediastinal mass adjacent to main pulmonary artery in 49 year old woman. (*B*) Small asymptomatic thymoma projecting to the right from the mediastinum in the vicinity of the right atrial appendage in 41 year old woman with myasthenia gravis.

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* From the Department of Radiology, Columbia University, College of Physicians and Surgeons, and the Radiological Service of the Presbyterian Hospital in the City of New York.

TABLE I

INITIAL EVENT LEADING TO DISCOVERY OF THYMOMA

	Patients with Myasthenia Gravis	Patients without Myasthenia Gravis
Routine chest roentgenogram: (9 patients with myasthenia gravis with no histologic examination of tumor)	32	14
Chest pain		4
Pleural effusion	1	2
Cough		2
Superior vena caval obstruction		1
Pericardial effusion		1
Autopsy	8	
Total Thymomas..........65	41	24

(third pharyngeal pouch) origin and the lymphocytes, can present in an extremely wide variety of combinations. Consequently, pathologic classification is difficult. The presence or absence of encapsulation and/or gross invasion has more prognostic value than has histologic classification. In addition, the ultimate prognosis of the patients with myasthenia gravis is much more related to the course of the myasthenia itself than to the behavior of a thymoma which may be present.

Lattes[17] of the Department of Surgical Pathology of the Columbia-Presbyterian Medical Center has recently reported an excellent detailed clinicopathologic study of these thymomas and others. He has classified the thymomas into a number of histologic types including: predominantly lymphoid, predominantly epithelial, predominantly spindle cell and rosette forming types. Some pathologists use the term "mixed type" for those tumors failing to display an obviously predominant cell type, while others prefer not to subclassify thymomas.

In myasthenia gravis, the thymomas are most commonly lymphoid in type, although the mixed and epithelial types are frequently seen. Since ionizing irradiation and adrenal steroid administration are particularly effective in destroying lymphocytes, had some of the histologic studies not followed irradiation or the stress of severe myasthenia gravis, even a larger number of predominantly lymphoid tumors would probably be found. Although seldom seen with myasthenia gravis, the spindle cell type of thymoma is often found in thymomas associated with aregenerative anemia or acquired hypogammaglobulinemia (Fig. 9, *A* and *B*).

CLINICAL FEATURES

The thymomas are best considered in two groups, depending upon whether or not they are associated with myasthenia gravis. A variety of initial events first indicated the presence of a thymoma—the most common being recognition of an anterior mediastinal mass on a routine chest roentgenogram (Table I).

TABLE II

AGE AND SEX DISTRIBUTION

			Age Groups						
			5–15	16–25	26–35	36–45	46–55	56–65	66–75
With myasthenia gravis	Males	13			1	5	4	3	
	Females	28		1	9	6	5	6	1
Without myasthenia gravis	Males	14	2	0	1	1	9	1	
	Females	10		1	1	1	3	4	
Totals		65	2	2	12	13	21	14	1

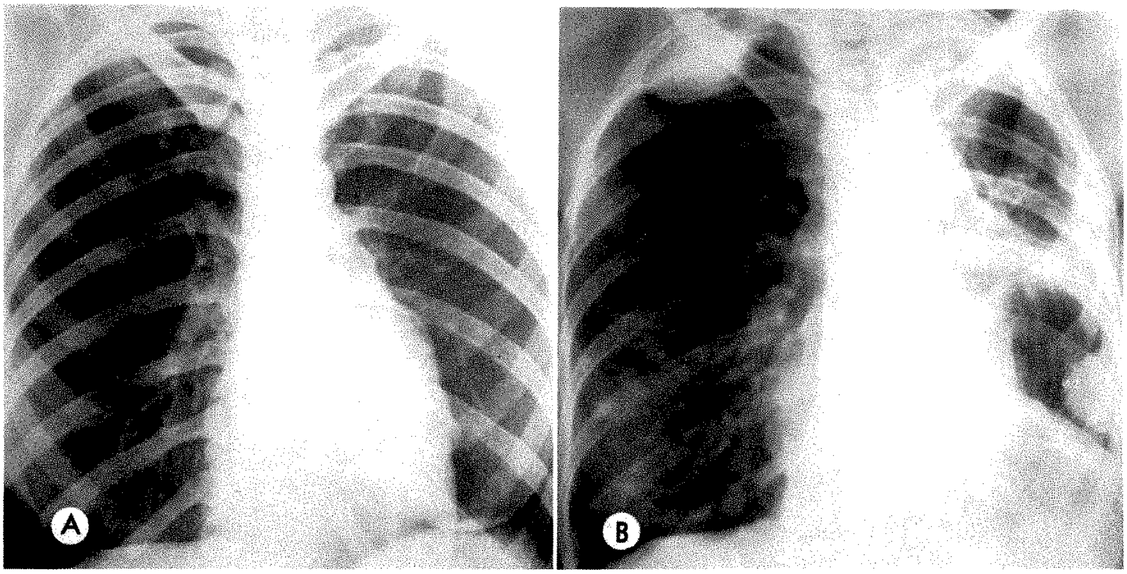


Fig. 2. (*A*) This lobulated left paracardiac thymoma in a 35 year old Negro woman was completely resected. (*B*) The tumor recurred and by 8 years later, despite reoperation and radiation therapy, the uncontrolled tumor had extended throughout the mediastinum and had invaded both lungs and pleural spaces. Large pleural implants are easily seen.

Fifty-six of these 65 patients were of Caucasian origin, 7 were Negroes and 1, a 7 year old Chinese boy. The age distribution of these patients is shown in Table II.

The thymomas found in patients without myasthenia gravis were more aggressive than those in patients with myasthenia gravis—at least in part because they were generally larger when first discovered and could be observed longer after treatment because of the absence of myasthenic deaths. Eighteen of these 24 thymomas were subject to gross total surgical removal, though 2 of these tumors recurred after intervals of 2 and 3 years, respectively, and may eventually cause death (Fig. 2, *A* and *B*). One patient refused operation, and the other 5 tumors could not be completely resected and were subsequently treated by radiation therapy. One of these patients has apparently been cured by radiation therapy (Fig. 8, *A* and *B*); another patient has persistent tumor after 8 years, and in the other 4 death was caused by local thoracic spread (1 month, 2 months, and 7 years following biopsy, and after 9 years in the patient refusing operation). Among these patients, 3 have had pericardial effusions, 2 have had superior vena caval obstruction, and 9 have had pleural effusions. Only one of these complications (a pleural effusion) occurred among the 16 patients apparently cured by resection. One of the patients who died had two small liver metastases, but none of the other patients were known to have tumor outside the thorax.

In myasthenia gravis the relationship of the thymoma to the patient is quite different. In 20 of the 23 patients surgically explored, total gross tumor removal was possible, though in 6 of these cases the tumor was densely adherent to adjacent structures, including the lung, being actually invasive in several cases. One of the patients with a nonresectable invasive thymoma is living after 7 years, but with persistent myasthenia gravis and a progressively invading tumor that threatens to cause death. Another patient with an incompletely resected tumor has a small asymptomatic pleural implant after 3 years of observation. The other patient with a nonresectable invasive tumor presented a different clinical problem in that the myasthenia gravis first became manifest 2

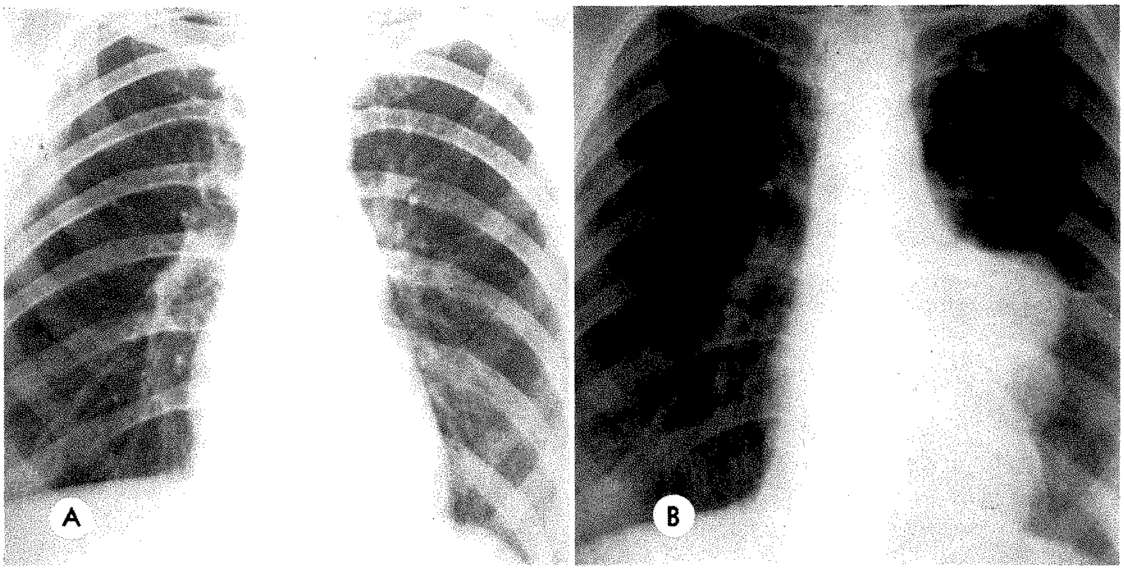


Fig. 3. (*A*) Normal chest roentgenogram of 48 year old white woman at beginning of spontaneous complete remission from myasthenia gravis which had been present for 6 years. (*B*) Eight years later this chest roentgenogram, obtained because of left-sided pleurisy, revealed this large lobulated left paracardiac thymoma. Though locally invading lung, the tumor could be completely resected, and the patient has remained well during the subsequent 4 years, still in remission from myasthenia gravis.

months prior to death—9 years after tumor biopsy. Only 1 of the other 38 patients with myasthenia gravis has had symptoms (an initial small pleural effusion) related directly to their thymomas (Fig. 3, *A* and *B*). This may be because 26 of the total of 41 patients have died as a consequence of myasthenia gravis (2 postoperatively). Twelve of the 15 survivors have persistent myasthenia gravis, which in 3 patients has considerably improved, after surgical resection in 2 and radiation therapy in the other. Two patients have had long remissions after tumor resection, while the final patient had already been in complete remission for 8 years before tumor resection was performed and has continued in complete remission in the 4 years following tumor extirpation (Fig. 3, *A* and *B*).

Three patients who died with myasthenia gravis had had known thymic tumors before myasthenia developed, 2, 9, and 20 years respectively (Fig. 4, *A–D*), although in only 1 of these was the tumor (but not the rest of the thymus) resected prior to onset of myasthenia. All of the other patients already had myasthenia gravis when their thymomas were first discovered, and this was usually when first looked for early in the illness, although in 5 cases the tumor first appeared a number of years later. The causes of the well-known association of myasthenia gravis and thymic abnormalities including thymic lymphoid hyperplasia and thymoma are not well understood,[5,11,21] though this association is regarded by some as evidence supporting the concept of myasthenia gravis as an "autoimmune" disease.[4]

ROENTGENOGRAPHIC FINDINGS

All of the thymomas in this series were predominantly in the anterior mediastinum with the exception of 1 tumor which arose in the subpleural tissues of the chest wall. About half of the tumors appeared at least somewhat lobulated, reflecting the characteristic lobulation and frequent cyst formation in the gross tumors. The remainder of these tumors were round, oval or plaque-like in shape. Curvilinear calcification

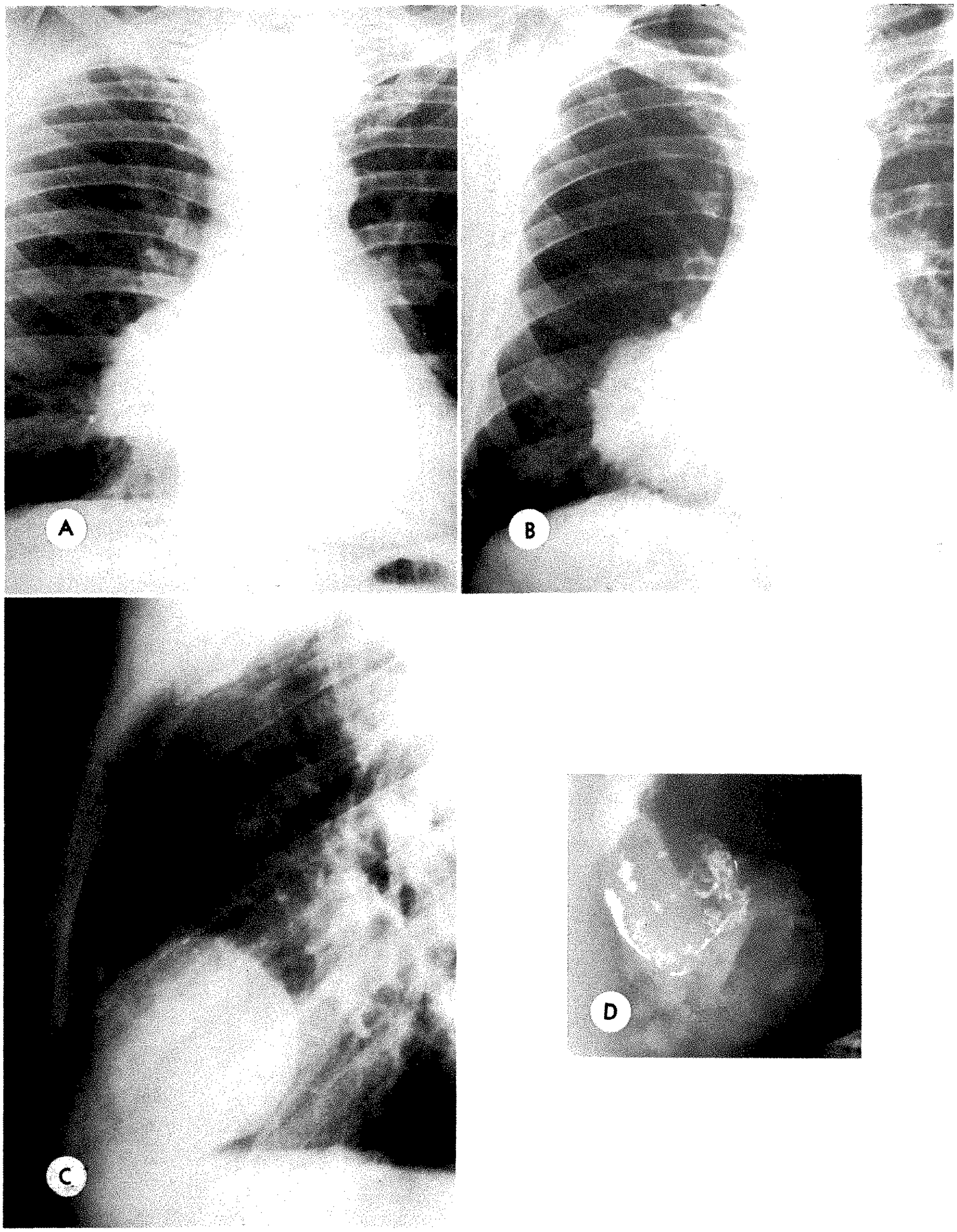


Fig. 4. (*A*) Right paracardiac mass on routine chest roentgenogram of asymptomatic 29 year old man. (*B*) Twenty years later at the time of onset of myasthenia gravis, the tumor was somewhat larger. (*C*) Lateral roentgenogram showing large mass in right pericardiophrenic angle. (*D*) Roentgenogram showing curvilinear calcification in resected tumor. Unfortunately, death in myasthenic crisis occurred one week postoperatively.

(Fig. 4*D*) was seen in 4 cases, none showing the more diffuse calcification mentioned by Bernatz *et al.*[2] as sometimes occurring in invasive tumors. Eighty per cent of the tumors arose at the level of the base of the heart, the others being scattered cephalad or caudad to this level. The tumors varied in size from huge masses mimicking massive cardiomegaly or aneurysm (Fig. 5, *A* and *B*) to tiny structures weighing under

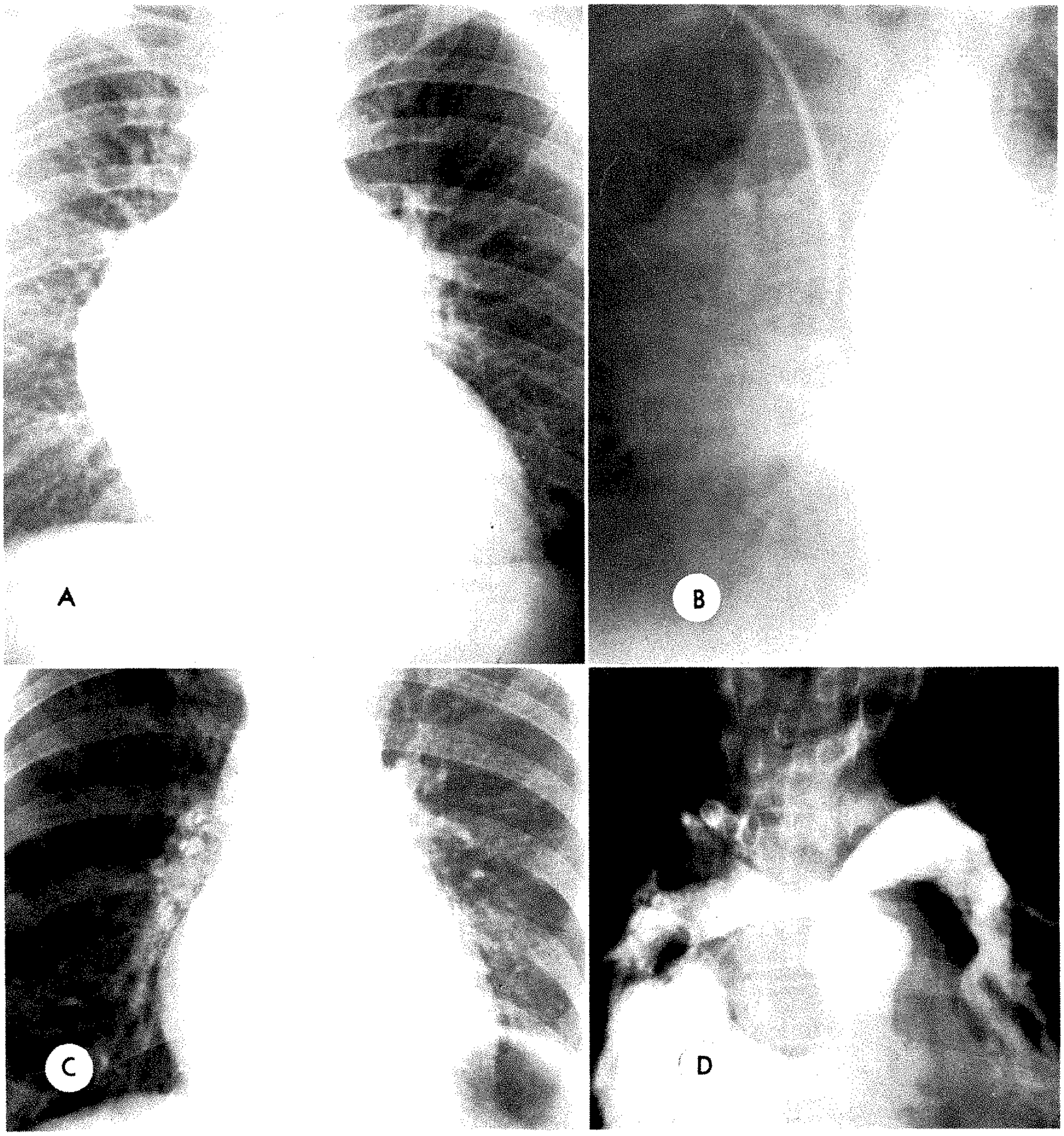


FIG. 5. (*A*) Frontal roentgenogram demonstrating huge right paracardiac mass in asymptomatic 26 year old man. (*B*) An angiocardiogram excluded the possibility of aortic aneurysm. The large thymoma which invaded pericardium and crossed the midline was completely resected. (*C*) This chest roentgenogram failed to reveal a mediastinal mass in a 57 year old woman who had had severe chest pain for 10 years, a large pericardial effusion 1 year before, and recent pleural effusions and symptoms suggestive of constrictive pericarditis. (*D*) The possibility of neoplasm was not considered until this angiocardiogram demonstrated severe compression of central pulmonary arteries. Death due to extensively invading mediastinal thymoma followed within 3 months despite radiation therapy.

3 gm. Only 4 of the tumors presented obviously on both sides of the mediastinum, all of which were invasive. In 6 invasive tumors gross pleural implants were recognized roentgenographically.

In the absence of myasthenia gravis, the possibility of thymoma is not usually considered until an anterior mediastinal mass is clearly identified on chest roentgenograms. In only 2 cases was visualization of the mediastinal tumor a problem. Both were invasive tumors: one presenting with a pericardial effusion was not recognized as a neoplasm until angiocardiograms demonstrated compression of the superior vena cava and pulmonary arteries (Fig. 5, *C* and *D*), and the other presenting with right pleural effusion and pleural implants which obscured the mediastinal mass. Obviously, pleural effusions or nodules, pericardial effusion, great vein obstruction, and involvement of lung are features of an invasive tumor and imply a poor prognosis.

About 1 in 8 patients with myasthenia gravis has a thymoma. This represents an incidence of about 5,000 times that in patients without myasthenia gravis. Consequently, the most minimal abnormality in the anterior mediastinum of a patient with myasthenia gravis must be regarded as a thymoma until proved otherwise. Twenty years ago when thymectomy was first advocated as a treatment for myasthenia gravis, many radiologists were chagrined to learn that thymomas were resected which were not diagnosed preoperatively. This led to the excellent roentgenographic studies of Good,[10] Harper,[12] and Robbins,[20] and more elaborate roentgenographic techniques for detection of these tumors have been recommended, including fluoroscopy, roentgenography in multiple projections, stereography, laminagraphy, angiocardiography, pneumomediastinography, etc.

In this series 41 thymomas were found among about 350 patients with myasthenia gravis. Eight tumors were first diagnosed at necropsy. Four of these tumors were small or multiple, weighing less than 7 gm. and occurred in patients not fully studied roentgenographically; another tumor was obscured by a large aortic aneurysm, while the other 3 patients had no satisfactory chest roentgenograms prior to death.

The other 33 thymomas were first recognized roentgenographically but not without difficulty in some cases. Ten of these could not be identified on the frontal chest roentgenograms (Fig. 6*A* and 7*A*), although 8 of these could be suspected in lateral projection. Two tumors, though quite evident in frontal projection, could not be seen in the lateral view. Two tumors were first identified in oblique projections, and about one-third of the tumors were most impressively seen in this view (Fig. 6*B* and 7*C*). Undoubtedly, some of the tumors would not have been noticed, being considered slightly prominent main pulmonary arteries, atrial appendages, azygos veins, or pericardial fat pads in the absence of knowledge that the patient had myasthenia gravis.

During the past 7 years we have routinely examined patients with myasthenia gravis utilizing posteroanterior, lateral and oblique (at 20°) chest roentgenograms and lateral laminagrams of the mediastinum. Over 100 such examinations have been performed with detection of 18 thymomas. No known false negative or false positive diagnoses have been made, although about half of these patients have had direct examination of the mediastinum at surgery or necropsy. Some tumors, however, may have been overlooked, being too small or plaque-like to produce a distinct roentgenographic abnormality. In several cases an unusually dense anterior mediastinum in young women has been correctly interpreted as a large thymus gland without thymoma. Although no tumors were diagnosed by laminagraphy alone, this technique was found valuable in 8 cases in making an abnormal contour more substantial and convincing—especially in the presence of obesity when other projections were less adequate technically. Occasionally (4 times in this series) when the tumor margin resembled a prominent pulmonary artery, an atrial append-

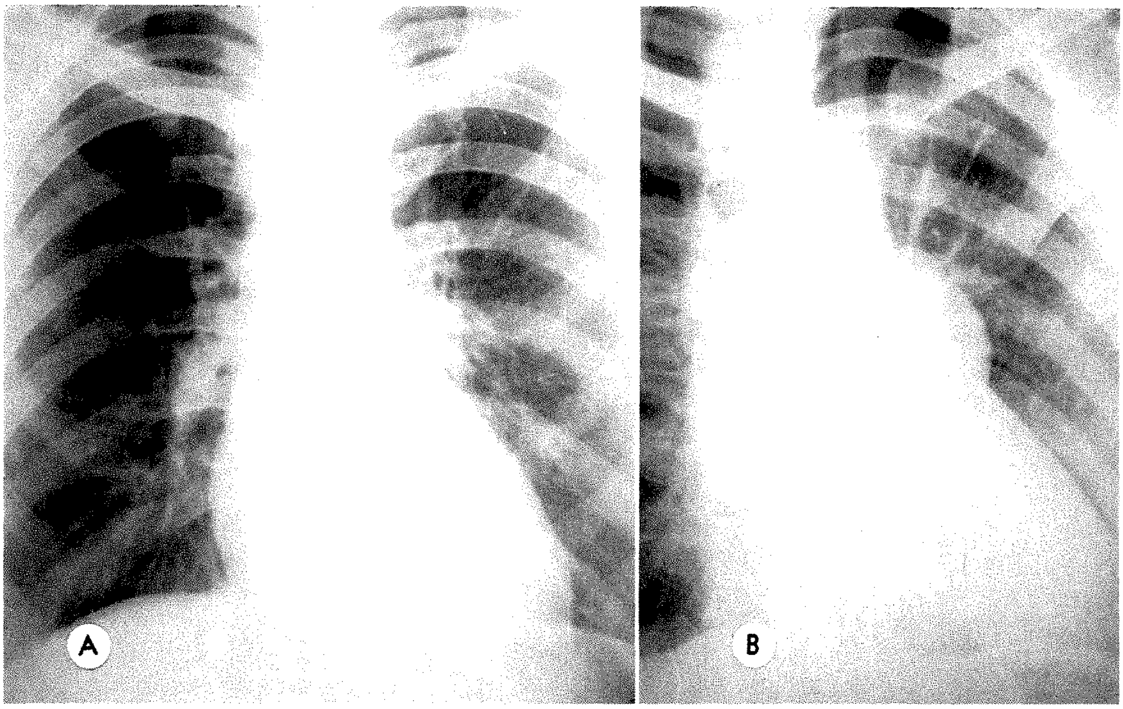


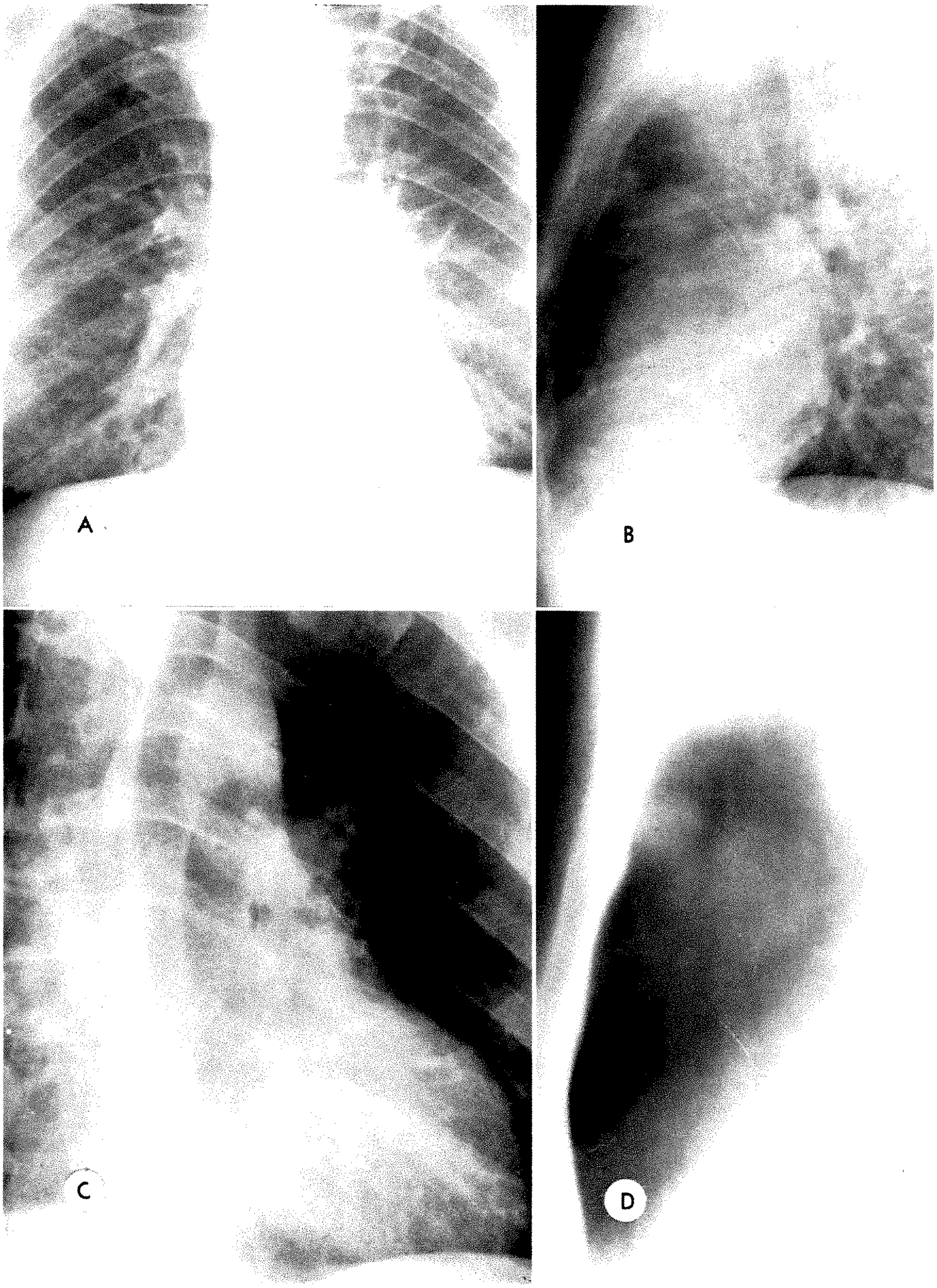
FIG. 6. (*A*) Normal frontal chest roentgenogram of 49 year old woman at onset of myasthenia gravis. (*B*) Right anterior oblique study clearly demonstrates a small thymoma overlying the main pulmonary artery (a tumor which was only questionably suspected in the lateral view).

age, a huge right atrium or an aortic aneurysm, venous angiocardiography has been helpful (Fig 5, *B* and *D*). We have not found fluoroscopy as useful as earlier investigators and have not been impressed by the value of pneumomediastinography in these fragile patients.

At present we believe that a satisfactory routine roentgenographic examination of the chest to detect thymomas in patients with myasthenia gravis should include the following projections: (1) posteroanterior stereoscopic, (2) left lateral, (3) right and left anterior oblique (at 20° obliquity), and (4) anteroposterior supine Bucky chest roentgenograms. Laminagraphy is not regarded as a necessary routine, but should be used liberally at the discretion of the radiologist to further investigate suspicious shadows of uncertain significance (Fig. 7*D* and 9*B*). *The most essential feature of the examination is that the radiologist is informed that the patient has myasthenia gravis.* The same type of investigation should be

»»→

FIG. 7. (*A*) Normal frontal chest roentgenogram of 51 year old white man 6 years after onset of myasthenia gravis. (*B*) Lateral roentgenogram suggesting a possible small mass in upper anterior mediastinum. (*C*) Right anterior oblique study clearly shows lobulated mass over main pulmonary artery. (*D*) Lateral laminagram of the mediastinum clearly demonstrates multinodular anterior mediastinal thymoma.


A
B
C
D

utilized in patients with aregenerative anemia or acquired hypogammaglobulinemia.

DIFFERENTIAL DIAGNOSIS

In the absence of myasthenia gravis, major differential diagnostic considerations in the roentgenographic diagnosis of the usual thymoma located in the anterior mediastinum include: lymphoma, teratoma, metastatic carcinoma, substernal thyroid or at times aortic aneurysm. A tissue diagnosis is required to exclude the first three possibilities. Substernal thyroid can usually be recognized by its high position in the mediastinum, its motion on swallowing, the clinical history and an I^{131} isotope scan. Angiocardiography is sometimes necessary to exclude aneurysm.

Among 350 patients with myasthenia gravis whom we have studied, 41 thymomas were found. Only 3 other anterior mediastinal masses were seen: a large aortic aneurysm, a substernal thyroid, and an area of paramediastinal pulmonary tuberculosis—all rather easily recognized because of clinical history and sequential chest roentgenograms.

EFFECT OF RADIATION THERAPY

Five of the 24 patients without myasthenia gravis had extensive, invasive inoperable thymomas that could only be biopsied. One of these patients is apparently cured 17 years after treatment of a large epithelial tumor causing superior vena caval obstruction with a tumor dose of 2,500 rads in 4 weeks (Fig. 8, *A* and *B*). One tumor, which completely regressed after 3,300 rads in 4 weeks, recurred 5 years later and again responded to radiation therapy but death resulted from persistent tumor and radiation pneumonitis. One thymoma was reduced only slightly in size after 3,000 rads in 5 weeks, but then could be almost completely resected. The other 2 patients died with extensive persistent invasive tumors within a few weeks following tumor doses of 2,100 rads in 6 weeks and 4,000 rads in 5 weeks, respectively.

In 3 cases tumor recurrences 2 to 5 years following surgical resections responded objectively by marked tumor regression after doses of 2,500 to 4,500 rads in 3 to 4 weeks, resulting in long periods of palliation but with persistent tumors which have not yet caused death 4, 8, and 10 years after operation (Fig. 2, *A* and *B*). Another patient who refused operation had a predominantly lymphoid thymoma (possibly initially resectable) which responded well to 1,600 rads in 10 days but recurred causing superior vena caval obstruction 7 years later, re-

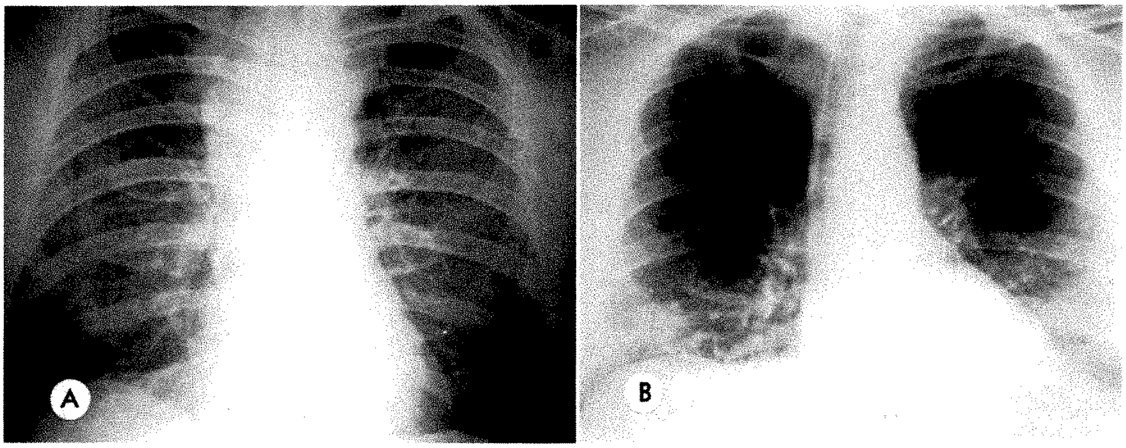


Fig. 8. (*A*) Frontal chest roentgenogram of 43 year old white man demonstrates a large inoperable superior mediastinal thymoma which had produced superior vena caval obstruction. Complete regression of tumor and symptoms followed radiation therapy (tumor dose: 2,500 rads in 4 weeks). Histologically, this was a definite thymoma predominantly of the epithelial type. (*B*) Seventeen years later the patient is asymptomatic and the chest roentgenogram is normal.

sponded again somewhat to two additional courses of radiation therapy and finally caused death after 9 years.

Among the 41 patients with myasthenia gravis, only 3 had incompletely resectable tumors (of 23 cases surgically explored). One of these patients, a 48 year old asymptomatic woman, had initially an excellent response to radiation therapy (3,000 rads in 3 weeks), but tumor recurred after 6 years causing superior vena caval obstruction, responded somewhat to additional irradiation but recurred, and finally severe myasthenia gravis became manifest 2 months before death and 9 years after the initial diagnosis. Another patient, a 40 year old woman with myasthenia gravis, experienced an excellent initial regression of the tumor following 5,000 rads in 5 weeks but after 5 years the tumor has recurred and may eventually cause death. The other patient with an incompletely resectable tumor has not yet been treated by irradiation. None of the 20 surgically resected tumors in this group has recurred although 12 of these patients have died of myasthenia gravis. Seven of the thymomas in patients with myasthenia gravis were treated only with irradiation: 3 small tumors treated with 4,000 rads in 4 weeks and another treated with 1,500 rads in 2 weeks decreased in size or disappeared on roentgenographic studies; 1 cystic tumor did not respond and 2 patients died of myasthenia gravis at completion of therapy before evaluation was possible.

It is clear that with moderate doses of radiation therapy most thymomas respond with a definite reduction in size, worthwhile palliation of aggressive tumors is often achieved, and in a few patients long term tumor control is obtained. Although one might expect the predominantly lymphoid thymomas to respond best to irradiation, our apparent cure involved a predominantly epithelial tumor. Supravoltage therapy has advantages in the treatment of thymomas but the optimal plan for treatment of these tumors is yet to be worked out.

SIGNIFICANCE OF THYMOMA IN MYASTHENIA GRAVIS

The practical significance of thymomas in patients with myasthenia gravis can be considered from several aspects: (1) prognosis related to tumor growth; (2) prognosis of concomitant myasthenia gravis; (3) value of radiation therapy; and (4) value of surgical resection.

As has already been shown, only 1 of the 41 patients in this series with thymomas and myasthenia gravis has died as a direct consequence of the thymoma (plus severe myasthenia gravis). Two others have persistent nonresectable tumors, but only 1 of these is an aggressively behaving tumor which is life-threatening at this time. These patients have been followed until death or if still living for an average of 7 years. Twenty-five have died as a consequence of myasthenia gravis and 1, as just mentioned, has died of invasive thymoma and terminal severe myasthenia gravis. Only 3 of the tumors have caused local symptoms. Since, once discovered, nearly all the thymomas were either resected or irradiated, the invasive potential of some tumors was undoubtedly obscured by treatment.

That thymomas associated with myasthenia gravis seldom are the cause of death is supported by observations in the literature.[2,7,11,16,20,23] For example, of 55 patients with myasthenia gravis and thymoma reported by Eaton and Clagett,[7] only 1 was known to die as a direct consequence of tumor invasion although 26 had succumbed to myasthenia gravis and 5 had died postoperatively.

In those few instances where the thymomas have caused death, initial detection of a mediastinal tumor was usually not difficult. In some of these rare patients, the myasthenia became evident only during the terminal illness caused by the neoplasm[19] (as in one of our patients). So far as the direct ravages of neoplasm are concerned, discovery of a very small or occult asymptomatic thymoma in a patient with myasthenia gravis is not likely to be of critical importance in the ultimate prognosis of the patient. From this viewpoint elaborate roentgenographic diagnostic techniques, especially those involving personal risk to these fragile patients such as pneumomediastinography, would not seem justified—especially when the additional diagnostic yield is very small or nil.

In general, as has been shown, myasthenic patients with thymomas tend to have severe myasthenia gravis with a relatively poor prognosis, whether or not the thymoma is resected.[7,11,16,20,23] The mortality due to myasthenia in these patients has ranged from 27 to 80 per cent. Because the results were so poor following thymoma resection in these patients, Keynes[16] and Williams[26] tried giving preliminary radiation treatment to these tumors prior to resection. Keynes[16] reported that of 20 thymomas treated by irradiation (up to 4,000 rads in 4 weeks) followed by resection in the years 1948 to 1953, the total mortality by 1953 had reached only 20 per cent and 12 of the survivors were much improved or in remission with respect to the myasthenia—results so encouraging that further trials in management along these lines are continuing, not only in London but also in Boston.[20] According to Keynes[16] (1955) "the necessity for avoiding primary operation (prior to irradiation of thymomas) underlies the importance of carrying out careful radiographic examination of every patient." Although radiation treatment preliminary to operative resection of thymomas may well be worthwhile, much more evidence is required before considering it of proved value with respect to the prognosis of the myasthenia.

Independent of the myasthenia gravis, in our experience radiation therapy in tumor doses of 3,000 to 4,500 rads in 3 to 5 weeks usually causes tumor shrinkage, occasionally completely destroys thymomas and can be a valuable therapeutic adjunct. Probably the radiation is most effective in destroying the lymphocytic cells in the tumors. Higher doses would more often destroy these tumors, but would also more often introduce serious radiation reactions in the lungs which can lead to death in these delicate patients. Adrenal steroids also have been shown to cause temporary shrinkage of some thymomas.[24] Since thymomas are in general slow-growing tumors, long follow-up periods are required for accurate evaluation of the results of treatment.

Although surgical resection of thymomas in myasthenia gravis is undoubtedly valuable in preventing further tumor growth and invasion and for this reason may be life saving in a few cases—the value of operation must be weighed against the operative risk. Since myasthenic patients with thymomas only occasionally die because of tumor invasion (5 to 10 per cent), a surgical mortality of around 10 per cent as reported in most large series might make one hesitate to recommend operation, especially for a small asymptomatic tumor. It is probable, however, that in experienced hands because of improvements in surgical techniques and in pre and postoperative care that the expected operative mortality is considerably less today (hopefully 2 to 5 per cent). Under these circumstances thymoma resection is justified from the standpoint of tumor control.

Occasional patients (such as the one with the first thymoma successfully resected by Blalock[3]) have experienced complete remission of myasthenia gravis following operation—so that some believe that resection is further justified for this reason[2]—particularly following preliminary irradiation of the tumor.[16]

Quite obviously, the decision for or against operation depends upon other factors, too, such as the patient's age, concomitant diseases, local circumstances, etc.

At present, substantial evidence suggests that thymectomy even in the absence of thymoma significantly improves the prognosis of certain individuals with myasthenia gravis—particularly young women.[7,16,20,23] Fragmentary evidence suggests that irradiation of the thymus in doses of 600 to 2,000 rads in 3 days to 2 weeks with or without subsequent thymectomy may also have value in controlling the myasthenia.[11,20,25] Should it be found that preliminary irradiation followed by thymic resection is the optimal treatment for myasthenia gravis—roentgenographic demonstration of small asymptomatic tumors in these patients would become unimportant.

THYMOMA AND ERYTHROID HYPOPLASIA

A peculiar association of thymomas, often of the spindle cell variety, with aregenerative erythrocytic anemia has been found in at least 37 cases.[1,13,14] Indeed, of all patients with this rare form of erythroid hypoplasia, approximately 50 per cent are said to have thymomas. These patients are almost all over 50 years of age and are usually females.

Of the reported cases, the red cell series was selectively involved in 20, with the others showing pancytopenia or thrombocytopenia, often as a late event in the course of the disease. Myasthenia gravis was present in 5 cases. Sixteen patients were subjected to thymectomy, and of these 8 exhibited a definite hematologic response. Three were cured by surgery alone, 3 responded only after further treatment including steroid therapy, and 1 had the onset of remission 4 years after thymectomy. One died shortly after surgery but had shown a good reticulocyte response with marked increase in hemoglobin before death. Two of our patients with thymoma had aregenerative erythrocytic anemia: 1 responding to thymectomy was previously reported;[14] the other, a 47 year old white woman, also had acquired hypogammaglobulinemia (Fig. 9, *A* and *B*).

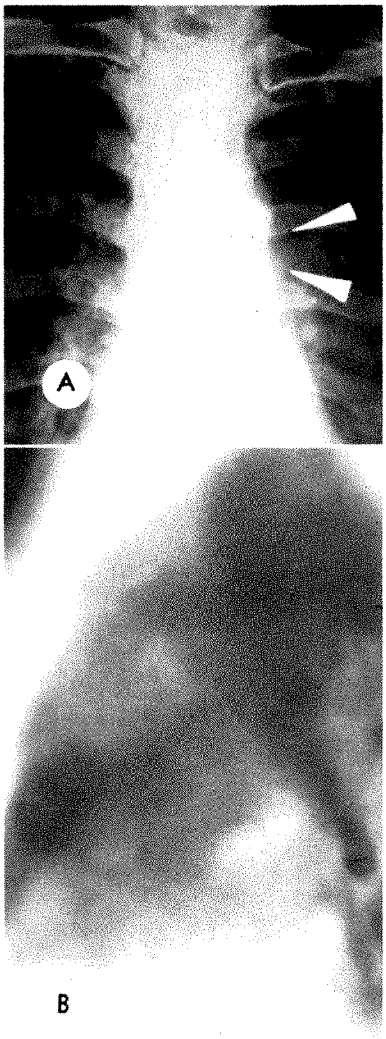


Fig. 9. (*A*) Frontal chest roentgenogram demonstrates faint convexity on left margin of mediastinum just below the aortic knob in a 47 year old woman with recurrent pulmonary infections for 5 years and severe refractory erythrocytic anemia requiring many transfusions for 18 months. (*B*) Lateral laminagram demonstrates the lobulated thymoma in the anterior mediastinum. Resection of this spindle cell tumor did not improve the anemia. One year later severe hypogammaglobulinemia was found just prior to death due to sepsis.

THYMOMA AND HYPOGAMMAGLOBULINEMIA

Another mysterious relationship is that between thymoma and acquired hypogammaglobulinemia; 5 to 15 per cent of patients with this rare protein abnormality may have thymomas.[9] At least 7 examples (5 women) of this association are known, including the case demonstrated here (Fig. 9, *A* and *B*). The ages ranged between 36 and 77 years. All but 1 have died of the consequence of severe infection. None of the 4 patients subjected to thymectomy was benefited. One of these patients had leukopenia, 2 had pancytopenia, and 1 had aregenerative erythroid anemia. All thymomas were present at the time of initial diagnosis of the hypogammaglobulinemia; and 3 were known to be present prior to the onset of frequent infections. All 6 of the tumors examined histologically were predominantly of the spindle cell type.

THYMOMA AND CUSHING'S SYNDROME

Thymoma associated with bilateral adrenocortical hyperplasia and consequent Cushing's syndrome has been described in a few cases, usually in men and usually diagnosed at necropsy.[6,22] The thymic tumors have been exclusively epithelial in type, devoid of lymphatic elements, as might be expected due to the known effect of adrenocortical hormones on lymphoid tissue. The special organoid pattern of these epithelial tumors is identical to that found in certain oat cell neoplasms of the lung (especially in their metastases) and in certain rare bronchial adenomas, both tumors which have also been associated with bilateral adrenal hyperplasia and Cushing's syndrome.[6] We have not encountered any thymomas of this type.

"GRANULOMATOUS" THYMOMA

Some pathologists believe that a primary granulomatous tumor of the thymus, distinct from Hodgkin's disease exists.[17,18] These tumors usually present as large masses, more or less confined to the anterior mediastinum, and they spread more by local extension than by systemic neoplastic proliferation of the reticuloendothelial system. The tumors appear to arise from thymus and not from lymph nodes, and, histologically, granulomatous and sclerotic foci are seen which are quite similar to those seen in Hodgkin's disease. Our surgical pathologist, Dr. Lattes,[17] believes that the "Dorothy-Reed" cells of these cases might originate from thymic epithelium. These giant cells contain PAS positive granules as does thymic epithelium, whereas the Dorthy-Reed cells of Hodgkin's disease do not contain such granules.

Although these tumors may occur in men, the 7 of this type that we have seen have all occurred in young women. Four of these patients died after a clinical course consistent with conventional Hodgkin's disease. The other 3 patients are living and well after minimal observation periods of 6 years following treatment by radiation therapy alone (2,400 rads in 3 weeks followed in 6 months by 2,400 rads in 2 weeks), surgery alone and by both modalities (4,000 rads in 4 weeks), respectively.

"SEMINOMA-LIKE" THYMOMAS

Rarely, tumors histologically identical to seminoma arise in the thymus in the absence of a demonstrable gonadal primary lesion.[15,17] The embryologic mechanism for the origin of such tumors (as well as of frank teratomas arising in this region) is disputed. Some feel that migratory germ cells are responsible for these neoplasms while other authorities believe that it is possible for such tumors to arise primarily from thymic tissue.

These tumors occur almost exclusively in young adult males as large lobulated anterior mediastinal masses which are locally invasive and may involve regional lymph nodes. Symptoms are produced by encroachment upon and adjacent mediastinal structures. When only seminomatous tissue is found in these tumors, they seem to have a relatively good prognosis, responding well to surgery and/or radiation therapy. We have encountered 5 such cases, 4 of which are alive and well with follow-up periods of 2 to 6 years. One died post biopsy with airway obstruction by tumor. Two patients treated locally with radiation therapy (4,000 rads in 4 weeks) because of incomplete resection are well, 3 and 5 years respectively following treatment.

SUMMARY

Experience with 65 thymomas is reported with attention to roentgenologic considerations.

More than half of these tumors (41) were found in patients who had or later developed myasthenia gravis. In myasthenia gravis the tumors seldom produced local symptoms and were often so small that roentgenographic detection depended upon recognition of very slight abnormalities in the anterior mediastinum. These thymomas rarely caused death, the myasthenia gravis being much more important in determining patient prognosis.

The thymomas not associated with myasthenia gravis were discovered because of

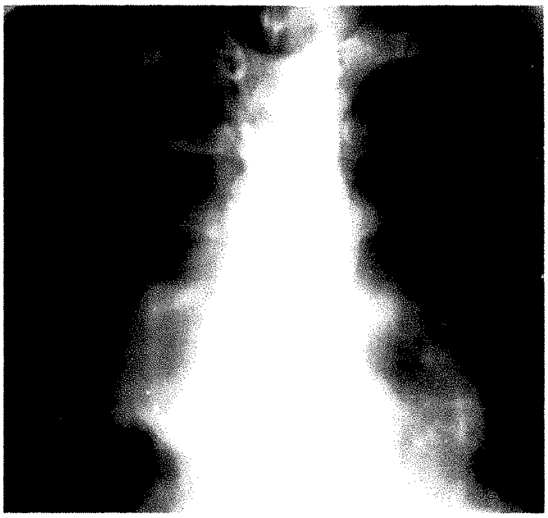


Fig. 2. Laminagram more clearly demonstrates the shape and sharply circumscribed margins of the posterior mediastinal mass.

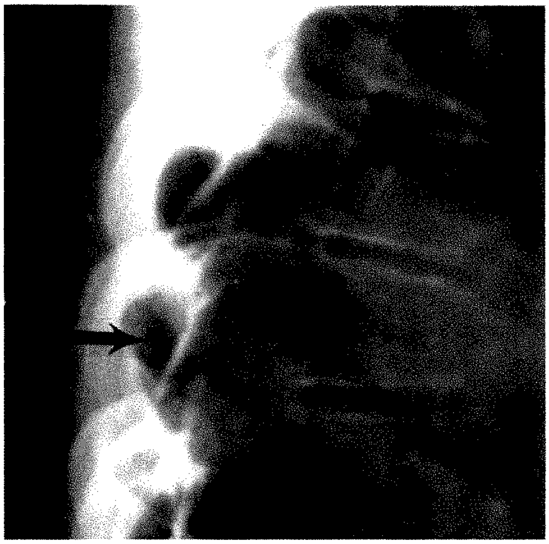


Fig. 3. Lateral roentgenogram of the mid-thoracic spine reveals definite erosion and enlargement of the right sixth intervertebral foramen.

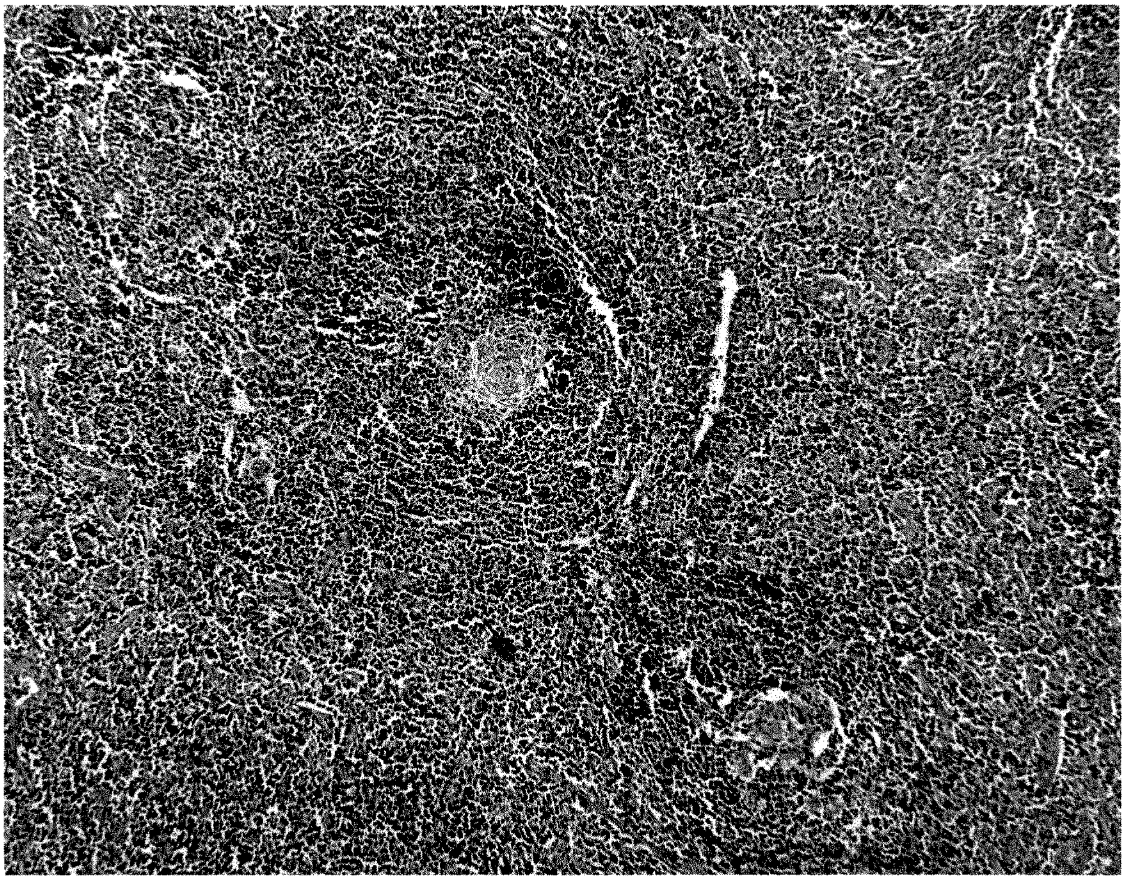


Fig. 4. Photomicrograph shows mass of lymphoid tissue with relatively rich vascular stroma and structures resembling Hassall's corpuscles.

laboratory data were unrevealing. Roentgenographic studies demonstrated scarring in the parenchyma of the superior segment of the right lower lobe. Minimal tubular bronchiectasis was demonstrated in the same segment by bronchography and these changes were thought to be the result of the previous irradiation. No definitive therapy was prescribed and the patient remained free of symptoms.

Because of the striking similarity of the roentgenographic findings in this case to that reported by Katz and Dziadiw, the pathologic material was reviewed. It was felt that the previous diagnosis of lymphosarcoma was incorrect and that the lesion actually represented benign mediastinal lymph node hyperplasia.

DISCUSSION

Castleman *et al.*,[1] in 1954, pointed out the existence of massive mediastinal lymph node hyperplasia in discussing the pathologic nature of an anterior mediastinal mass which had roentgenographic and pathologic characteristics similar to a thymic tumor. He and his associates[2] subsequently reviewed a large number of supposed thymic tumors and discovered 12 additional instances of enlarged mediastinal lymph nodes resembling thymic tumors pathologically. Cohen[3] has since added 2 other cases —one, a tumor occurring in the superior mediastinum, while the other was found in the substance of the deltoid muscle. Inada and his co-workers[4] have located 5 such similar lesions, all occurring in the mediastinum. Lattes and Pachter[7] have recently studied the pathologic aspects of 12 such lymphoid masses apparently not arising in lymph nodes. Four were located in the mediastinum, 3 of which were in the posterior mediastinum (including the case being presented); 5 were found in the soft tissues of the neck and shoulder, 1 in the retroperitoneal space and 2 within skeletal muscles. Jamplis and his group[5] have reported an

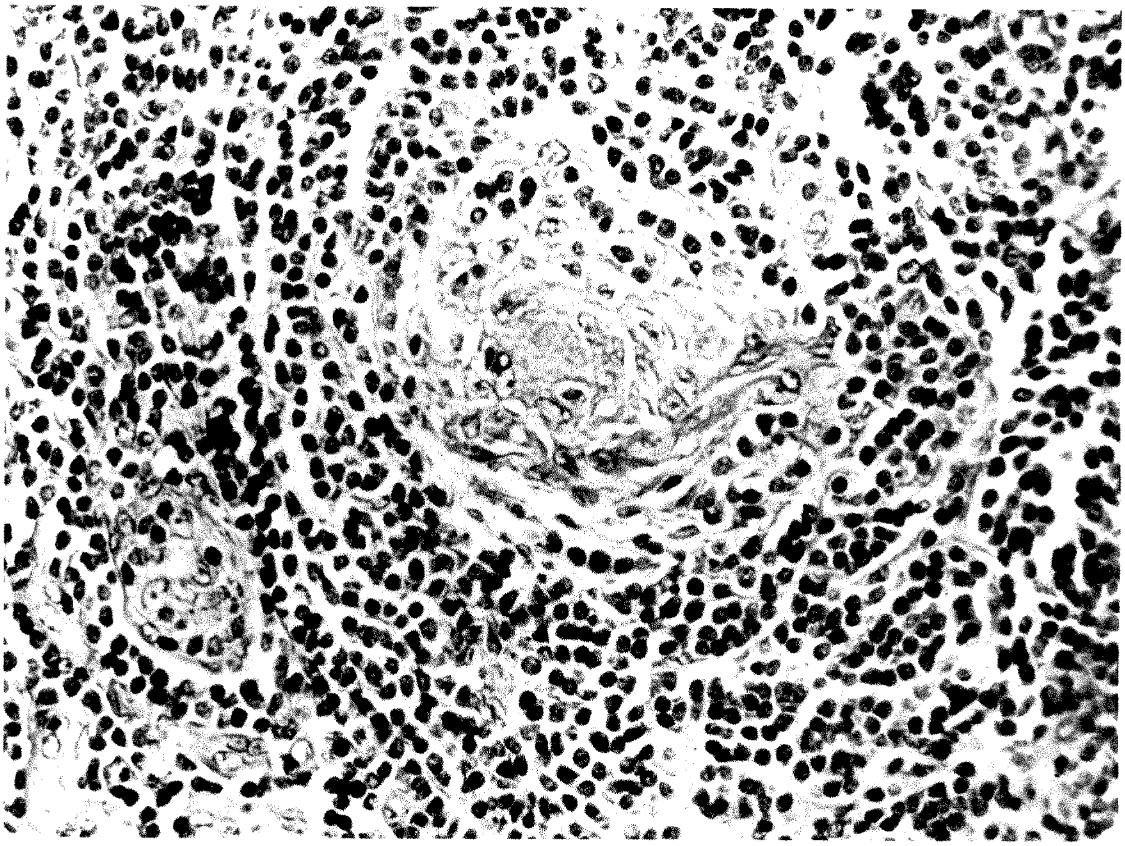


FIG. 5. Cluster of epitheloid cells forming an aggregate suggestive of Hassall's corpuscle (×425).

local symptoms or more often as unexpected, usually obvious, anterior mediastinal masses on routine chest roentgenograms. Although thymoma is the most common surgical tumor of the anterior mediastinum, definitive diagnosis depends on histologic study. One quarter of these tumors are locally invasive and many others are densely adherent to adjacent structures. Surgical resection of most tumors is possible, including some of the invasive ones. Radiation therapy in moderate dosage usually causes tumor shrinkage but seldom completely destroys these tumors.

"Seminoma-like" and "granulomatous" thymomas as well as the peculiar associations of thymomas with aregenerative anemia, acquired hypogammaglobulinemia, and Cushing's disease are briefly considered.

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POSTERIOR MEDIASTINAL LYMPH NODE HYPERPLASIA*

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TUMORS of the posterior mediastinum with erosion of adjacent ribs and vertebrae are almost exclusively neurogenic in nature. Katz and Dziadiw,[6] however, have recently reported for the first time the presence of massive benign lymph node hyperplasia in the posterior mediastinum simulating a neurogenic tumor. This report prompted us to review the pathologic nature of an unusual posterior mediastinal lymphoid tumor removed several years ago at this institution, thought to be a lymphosarcoma. Re-evaluation of the histologic sections revealed it to be massive lymph node hyperplasia.

REPORT OF A CASE

This 16 year old white female was admitted to the University of Maryland Hospital in August, 1957, for treatment of a mass in the posterior mediastinum, detected 4 months previously on a routine chest roentgenogram. There were no symptoms referrable to the mass. The physical examination and laboratory data were not remarkable.

Roentgen examination of the chest revealed a 7X3X7 cm. mass, somewhat triangular in shape, situated in the right paravertebral gutter, eroding the posterior margins of the right sixth and seventh ribs as well as the lateral margin of the body of the sixth thoracic vertebra (Fig. 1 and 2). Definite enlargement of the right sixth intervertebral foramen (Fig. 3) was believed to be present. The tumor, roentgenologically, was thought with certainty to be neurogenic in nature, most likely a neurilemmoma.

Five days after admission, a right thoracotomy confirmed the presence of a well defined noninvasive mass in the posterior mediastinum, which was easily shelled from its bed, along with its attachment to the sixth thoracic nerve. Pressure erosion of the right sixth and seventh ribs was noted, but the tumor did not extend into the sixth intervertebral foramen. A frozen section of the tumor as well as the permanent histological sections were felt to be characteristic of lymphosarcoma. The postoperative course was uneventful.

Although the location and appearance of the tumor was thought to be most unusual for lymphosarcoma, the pathologic diagnosis was accepted. Following recovery from the surgical procedure, the patient was subjected to supervoltage (Co^{60}) radiation therapy. A tumor dose of 4,000 r was given in the area of the posterior mediastinum through parallel opposing portals.

The patient was followed carefully and was completely asymptomatic until August, 1960, at which time she experienced several episodes of hemoptysis in a 24 hour period. Although the bleeding did not recur, the patient was hospitalized. Physical examination and extensive

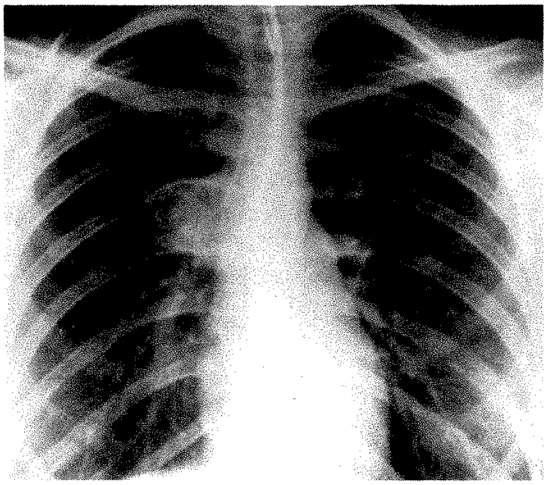

FIG. 1. Chest roentgenogram reveals triangular shaped mass located in right paravertebral gutter, causing erosion and reactive sclerosis of the posterior aspects of the right sixth and seventh ribs. Erosion of the right lateral margin of the sixth thoracic vertebral body is present, but is not detectable on this reproduction.

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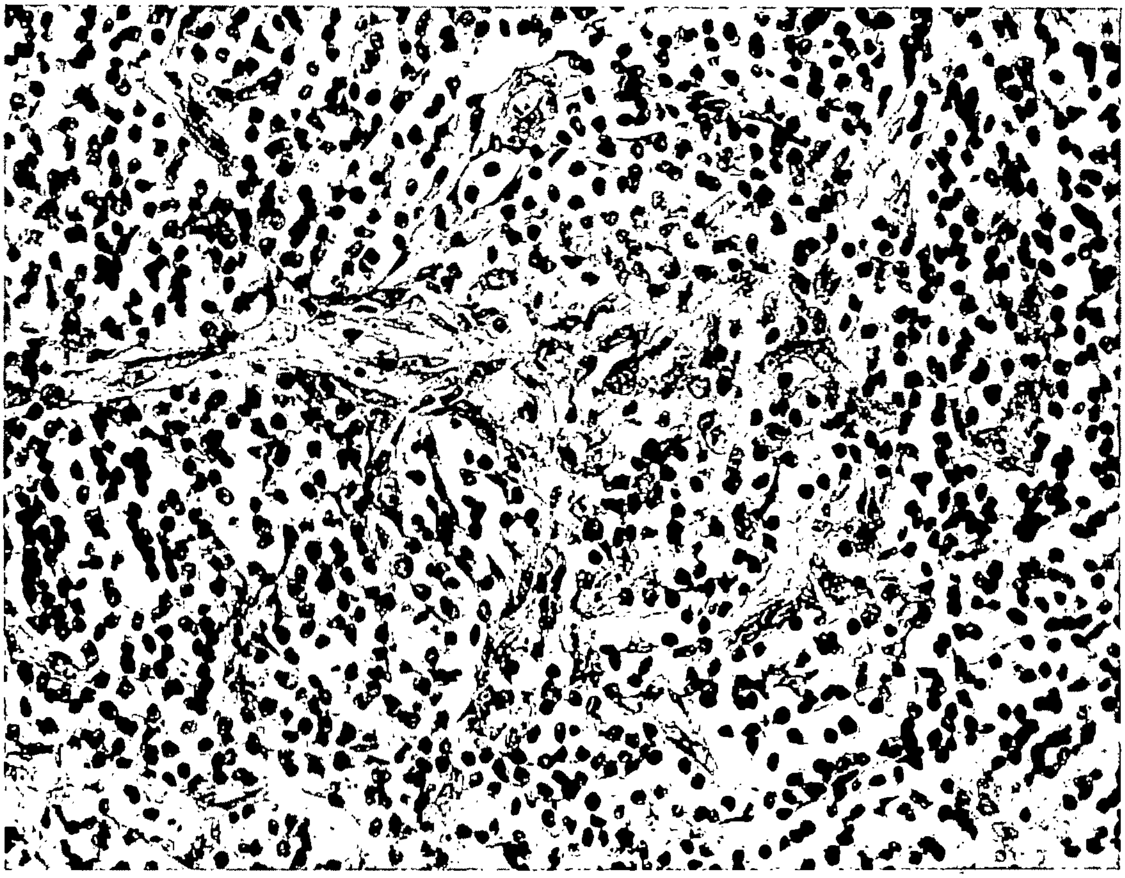

FIG. 6. Margin of mass showing anastomosing blood vessels surrounded by lymphocytes, suggesting an early stage in the formation of "pseudo-Hassall's corpuscles." The lymphocytes tend to line up along reticulin membranes, creating a concentric pattern not usually seen in malignant lymphoma (×425).

additional case, the mass in this case being located in the major interlobar fissure of the right lung.

The etiology of this unusual entity has not been established, but the prevailing opinion is that the proliferative changes in the lymph nodes reflect the presence of a chronic nonspecific inflammatory process. A specific organism or other causative agent has not been isolated. It has been stated that the process is that of hyperplasia rather than neoplasia, since the tumors are not locally invasive, nor do they metastasize or recur. Lattes and Pachter[7] are not in agreement with this etiologic explanation. Rather, they feel that the masses represent development or growth disturbances of lymphoid tissue with the lymphoid components organized in an abnormal fashion (hamartomas or choristomas). They emphasize the fact that these masses have occurred in areas where lymph nodes are not found.

The majority of the intrathoracic lesions occur close to the tracheobronchial tree at the lung root. Several have been reported in the anterior mediastinum and this report describes the fourth instance of such a tumor located in the posterior mediastinum. The lesion usually presents as a large single mass, but can be multinodular. Microscopically (Fig. 4, 5 and 6), the essential features are a marked proliferation of lymphoid and vascular tissue, with formation of some lymphoid follicles containing capillaries. Structures somewhat resembling epitheloid cell granulomas with Hassall's like corpuscles or germinal centers are seen, but keratin, as is found in Hassall's corpuscles of thymic tissue, is not present. The lymphocytes have small, round nuclei and appear benign, and true pathologic criteria of malignant lymphoma are not present in these lesions.

Clinically, the majority of patients reported are asymptomatic, the lesion having been detected accidentally. No age or race predilection has been noted, but they appear to be more common in females. The mass grows slowly and may even remain static, documented cases having been followed many years without change. Castleman and co-workers' original patient was known to have a mediastinal mass for at least 9 years. There is no recorded instance of local recurrence or dissemination of the process following surgery.

Roentgenographically, these tumors present as large well circumscribed homogeneous mediastinal or hilar masses which have no specific characteristics. They are indistinguishable from more common and better known lesions of various portions of the mediastinum and have been incorrectly diagnosed as thymomas, lymphomas or adenomas. In the posterior mediastinum, hyperplastic lymph nodes may simulate neurogenic tumors both grossly and roentgenographically even to the extent of causing erosion of adjacent osseous structures. As Katz and Dziadiw[6] pointed out, other lesions such as tuberculous spinal abscess, metastatic malignancy, bronchogenic carcinoma, chest wall neoplasm, mediastinal endothelioma and lipoma, extrapleural cyst and intrathoracic meningocele may, on rare occasions, cause changes in the posterior mediastinum that mimic tumors of nervous tissue. Benign lymph node hyperplasia must now be added to this group.

SUMMARY

An additional case of so-called benign massive mediastinal lymph node hyperplasia is reported. It is of interest to note that this is the fourth reported instance of this unusual entity in the posterior mediastinum and, as in the previous cases, gross pathologic and roentgenologic changes were present, indistinguishable from those usually associated with intrathoracic neurogenic tumors.

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OVAL-SHAPED CONSOLIDATIONS SIMULATING NEWGROWTH OF THE LUNG*

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PNEUMONIC consolidations frequently present unusual oval-shaped shadows on roentgenograms which may be mistaken for exophytic newgrowths of the lung.

The oval shape is largely due to the multisegmental distribution of these consolidations. This is caused by the spread of the process through interalveolar communications and lymphatics. The segmental bronchi themselves are open and not involved and the disease is confined to the small bronchi and the alveoli. These consolidations may be peripheral or arise adjacent to the hili and are usually within one lobe since the interlobar septa are barriers to this type of spread.

During the past year we observed several cases that presented with such large

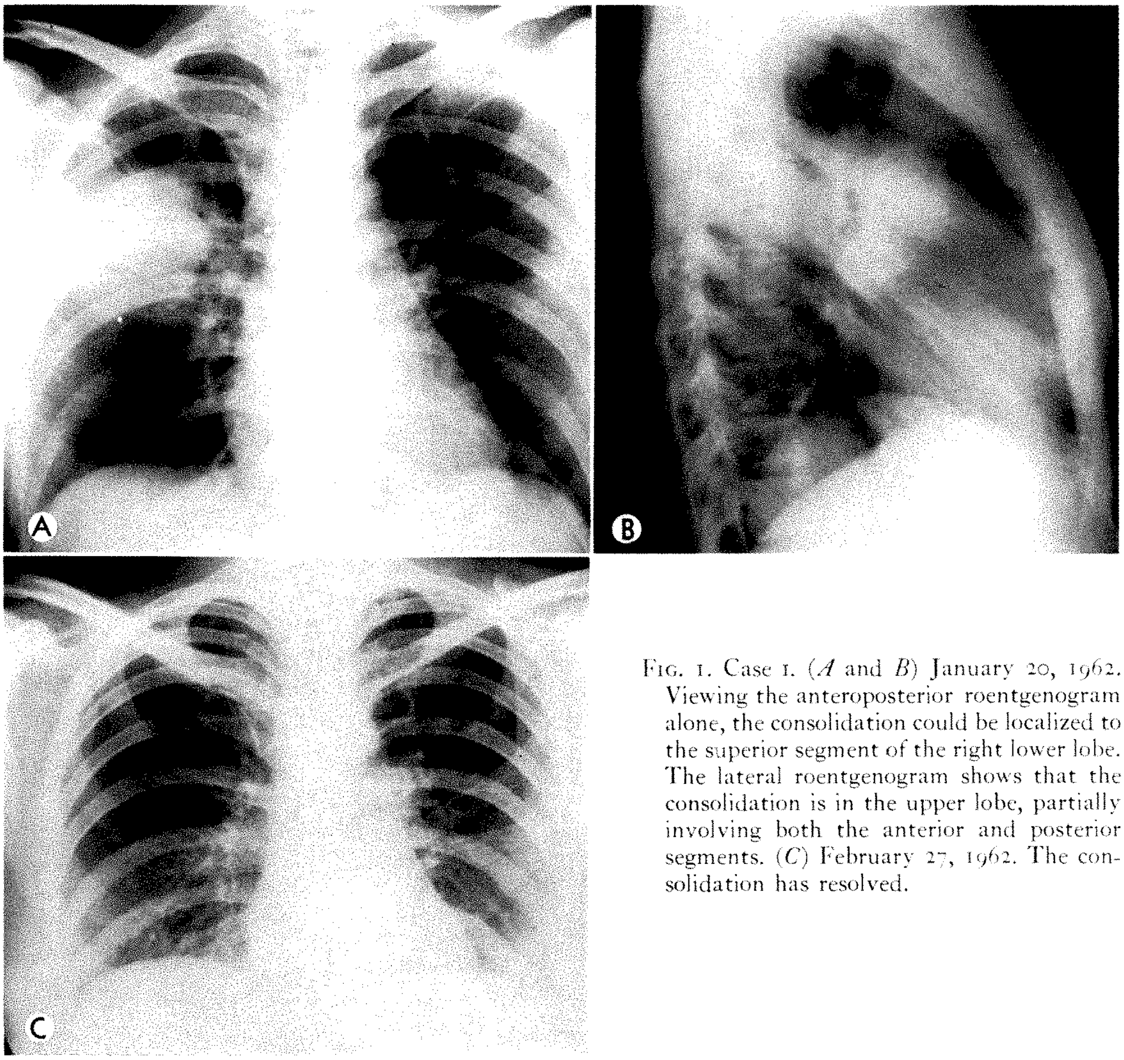

Fig. 1. Case 1. (*A* and *B*) January 20, 1962. Viewing the anteroposterior roentgenogram alone, the consolidation could be localized to the superior segment of the right lower lobe. The lateral roentgenogram shows that the consolidation is in the upper lobe, partially involving both the anterior and posterior segments. (*C*) February 27, 1962. The consolidation has resolved.

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round or oval shaped shadows on the initial chest roentgenograms. In many instances these shadows were thought to be pulmonary masses caused by malignant newgrowths but subsequently proved to be simple pneumonic consolidations.

The purpose of this paper is to call attention to multisegmental pneumonias and their pathogenesis, in general, and to emphasize the difficulties in differentiating them from pulmonary malignant neoplasms.

ILLUSTRATIVE CASES

Case. I. E.W., a 35 year old white female, was admitted to the hospital with respiratory distress of 1 week's duration. Her chest roentgenogram showed a round, well demarcated consolidation simulating a mass in the right upper lung field (Fig. 1*A*). Viewing the anteroposterior roentgenogram alone, the consolidation could be localized to the superior segment of the lower lobe. The lateral roentgenogram showed that the consolidation was in the upper lobe, partially involving both the anterior and posterior segments (Fig. 1*B*). The consolidation resolved after 5 weeks of antibiotic therapy (Fig. 1*C*).

Case II. R.O., a 50 year old white female, was admitted to the hospital because of cough and chest pain of 2 weeks' duration. The admission roentgenogram of the chest showed a round mass in the right mid-lung field and chronic tuberculosis, for which the patient has been previously treated (Fig. 2*A*). The "mass" was caused by incomplete consolidation of the medial segment of the right middle lobe. The consolidation resolved after 10 days of antibiotic therapy (Fig. 2*B*).

Case III. A.O., a 31 year old Negro male, was admitted to the hospital because of cough, fever and generalized weakness of 1 week's duration. The initial chest roentgenogram showed a large oval-shaped mass in the right upper lung field which was caused by incomplete consolidation of mainly the posterior and also the anterior segment of the right upper lobe (Fig. 3, *A* and *B*). The consolidation cleared slowly. A chest roentgenogram taken several weeks later showed complete disappearance of the "mass" (Fig. 3*C*).

Comment. The 3 cases in this group have several common features. All of them presented with relatively acute clinical histories and the chest roentgenograms revealed complete resolution of the consolidations within 3 to 4 weeks after initiation of antibiotic therapy.

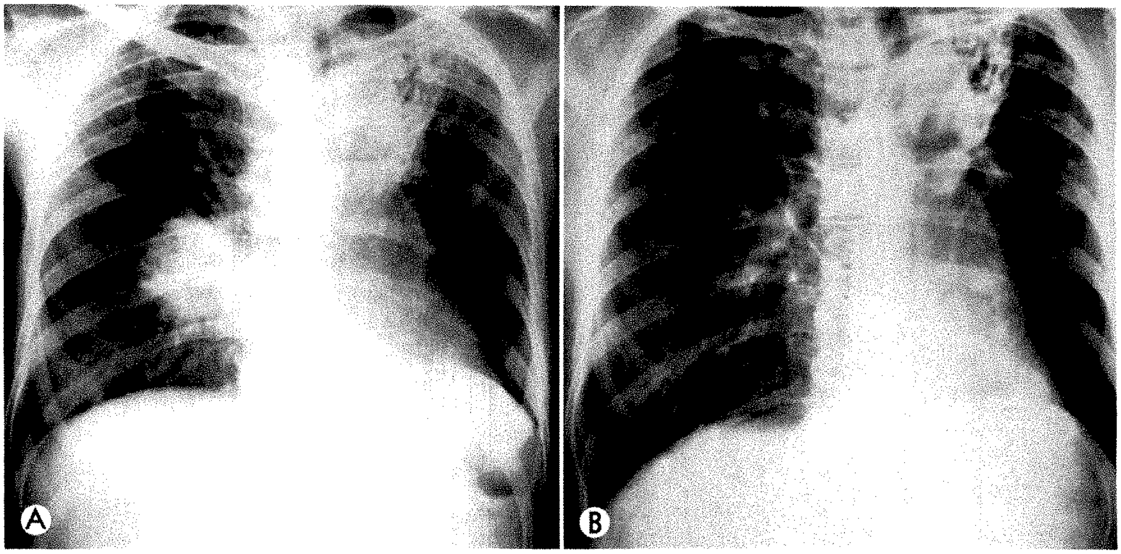

Fig. 2. Case II. (*A*) November 19, 1962. Round mass in the right mid-lung field caused by incomplete consolidation of the medial segment of the right middle lobe. The changes in the apices are due to chronic tuberculosis. (*B*) November 29, 1962. The consolidation has resolved.

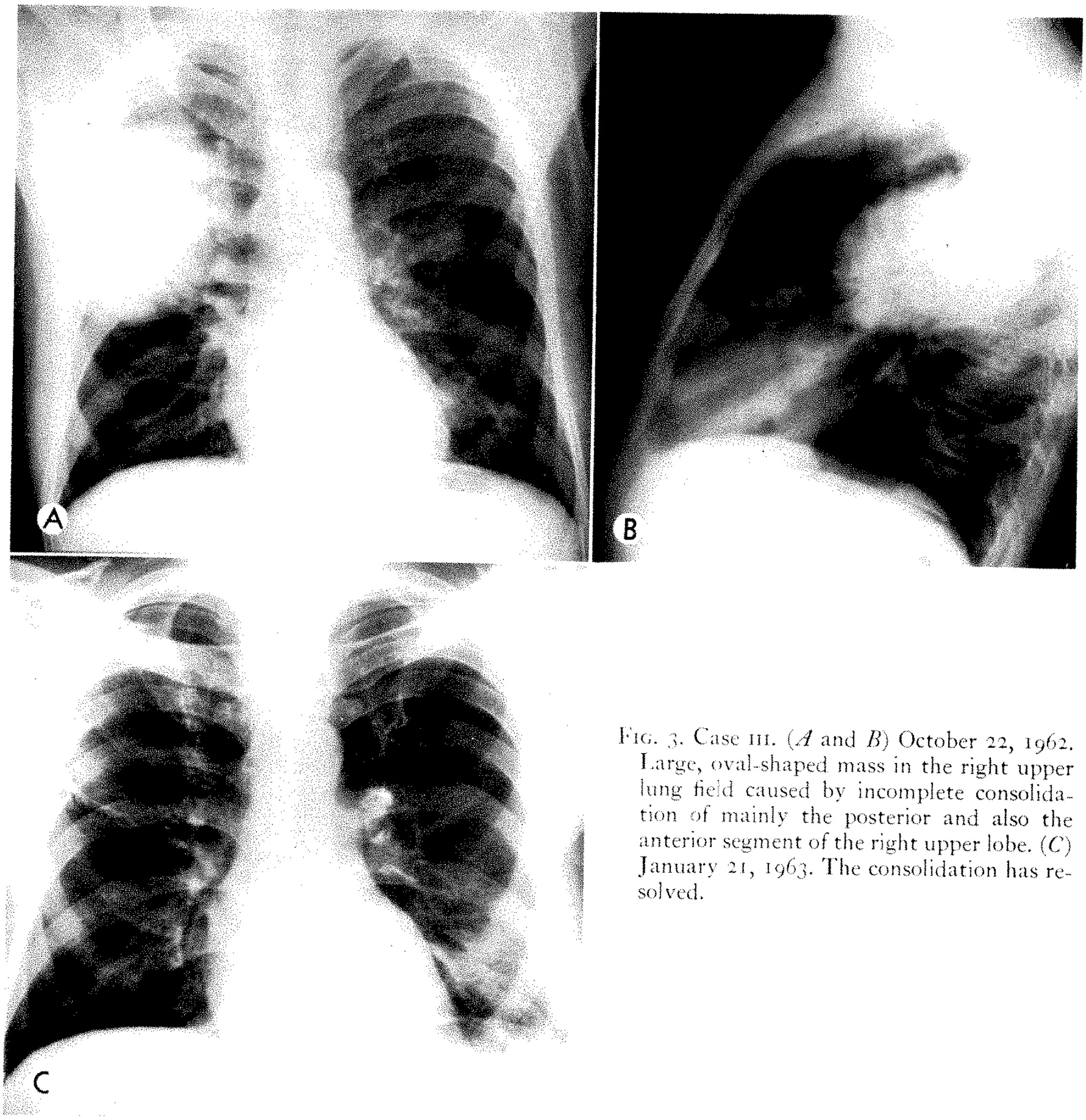

Fig. 3. Case iii. (*A* and *B*) October 22, 1962. Large, oval-shaped mass in the right upper lung field caused by incomplete consolidation of mainly the posterior and also the anterior segment of the right upper lobe. (*C*) January 21, 1963. The consolidation has resolved.

Cases i, ii and iii showed the typical roentgenographic appearance of multisegmental, oval shaped pneumonias and the initial roentgenograms could and did suggest tumor masses. In these cases the clinical histories were of decisive help, even before we realized the mechanism and frequency of multi- or nonsegmental distribution. However, the following cases will illustrate the fact that the clinical history may also be misleading.

Case iv. J.F., a 68 year old white male (a chronic alcoholic), was admitted with dyspnea cough and fever of 1 week's duration. There was no history of anorexia, weight loss or chest pain. The chest roentgenogram showed a large, homogeneous oval shaped mass in the left lower lung field (Fig. 4). The patient was thought to have extensive pneumonia and died a few days later, supposedly due to overwhelming pneumonitis. At autopsy a large bronchogenic carcinoma was found in the left lower lobe, corresponding in size and location to the mass seen on the chest roentgenogram.

Case v. P.L., a 38 year old Negro male, was

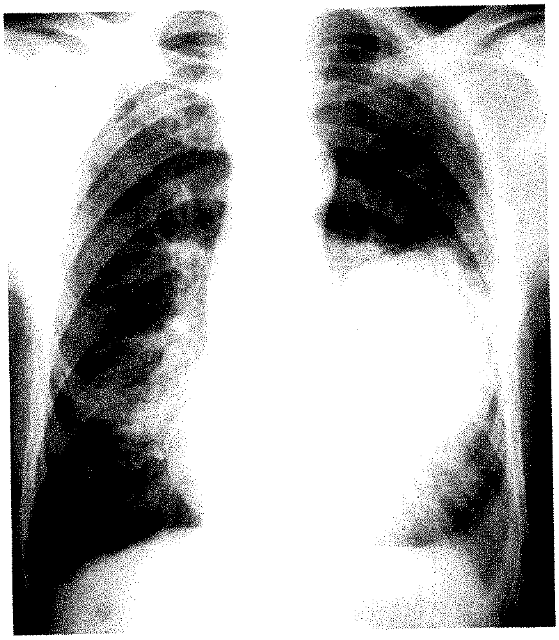

FIG. 4. Case IV. Large, oval-shaped mass in the left lower lung field. At autopsy a large bronchogenic carcinoma was found, corresponding in size and location to the mass seen on this roentgenogram.

admitted because of chest pain of several weeks' duration which worsened and the patient also became febrile 1 week prior to admission. His chest roentgenogram showed a round mass in the lower left lung field (Fig. 5*A*). One year before the present admission the patient underwent thoracotomy in another hospital, probably for a benign disease. The diagnostic work-up and antibiotic therapy were started simultaneously. Bronchoscopy, scalene lymph node biopsy and cytologic studies of the sputum were negative. After 5 weeks of antibiotic therapy, the "mass" finally resolved (Fig. 5*B*). This was a pneumonic consolidation, partially involving the posterior and lateral basal segments of the left lower lobe.

CASE VI. P.T., a 58 year old white male, was admitted because of chest pain, anorexia and weight loss of 3 months' duration. The physical examination at the time of admission was negative, though the patient had low-grade fever. The chest roentgenogram showed an oval shaped, lobulated mass in the right mid-lung field and an area of hazy infiltration and/or fibrosis in the right apex (Fig. 6*A*). The patient was started on antibiotics and his diagnostic work-up commenced with cytologic studies of the sputum. These were all negative. However, the "mass" responded well to the antibiotics and resolved completely after 6 weeks of therapy (Fig. 6*B*). The "mass" was caused by partial consolidation of the superior segment of the lower lobe and likewise partial consolidation of the lateral segment of the middle lobe. The two incompletely consolidated segments created the image of the lobulated, oval-shaped

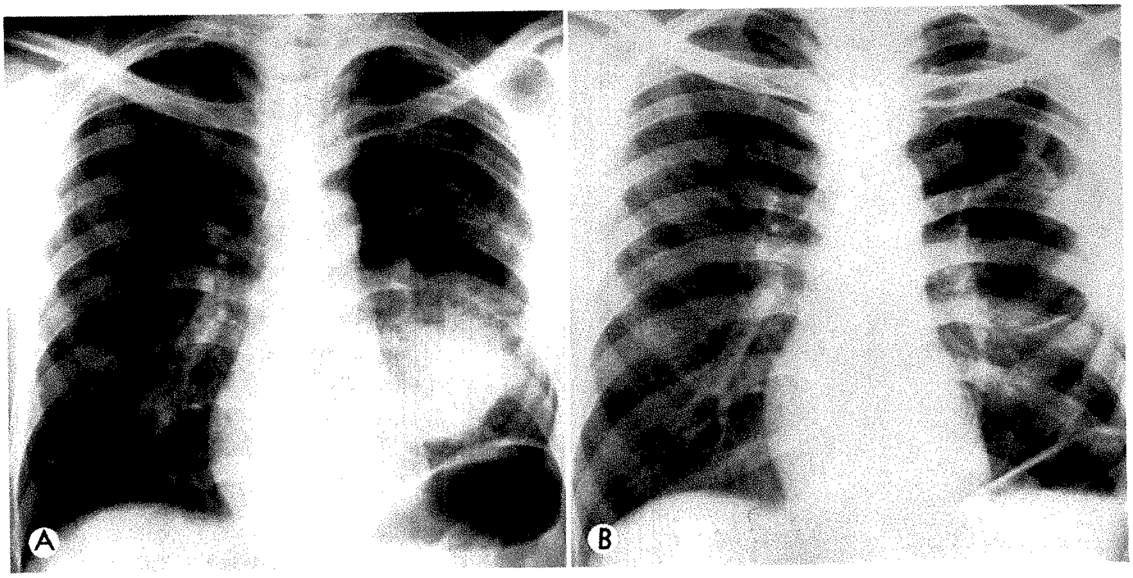

FIG. 5. Case V. (*A*) April 1, 1961. A round, sharply demarcated consolidation, partially involving the posterior and lateral basal segments of the left lower lobe, is demonstrated. (*B*) May 4, 1961. The consolidation has resolved.

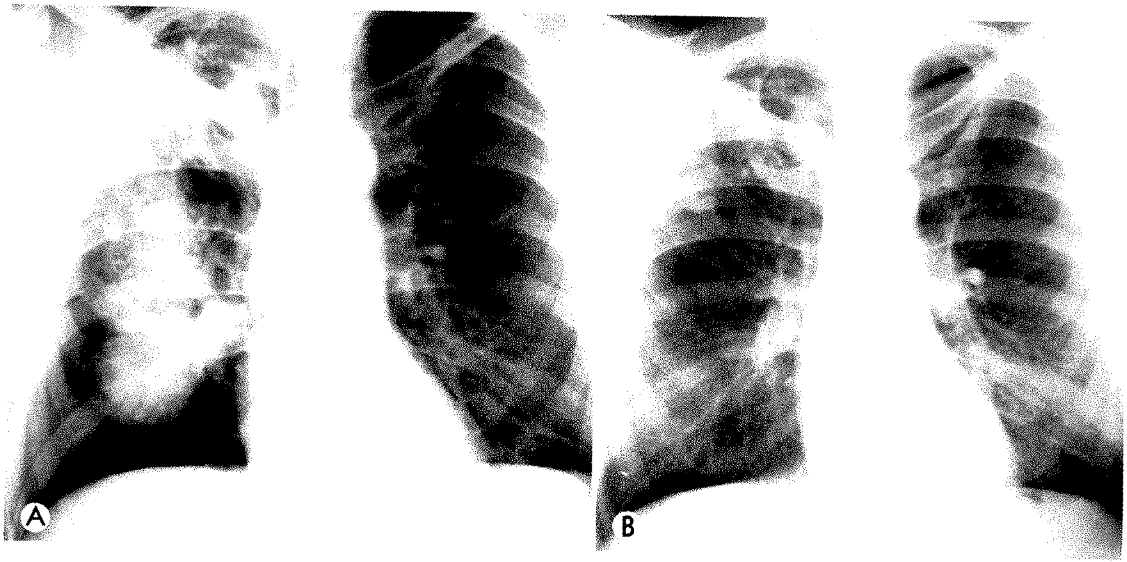

FIG. 6. Case VI. (*A*) December 26, 1961. Oval shaped, lobulated consolidation in the right mid-lung field, caused by incomplete involvement of the superior segment of the lower lobe and incomplete involvement of the lateral segment of the middle lobe. The changes in the right apex were due to chronic tuberculosis. (*B*) February 8, 1962. The consolidation has resolved.

mass. The hazy density in the right apex did not change and was probably due to fibrosis, caused by chronic tuberculosis.

CASE VII. F. F., a 58 year old white male, was admitted disoriented and intoxicated. His chest roentgenogram showed a homogeneous, oval-shaped consolidation in the right upper lobe, which left the medial peripheral portion of the lobe uninvolved (Fig. 7*A*). At admission the clinical diagnosis was pneumonia. The patient did not improve on antibiotic therapy and the chest roentgenogram showed no change after 2 weeks. Bronchoscopy was performed but failed

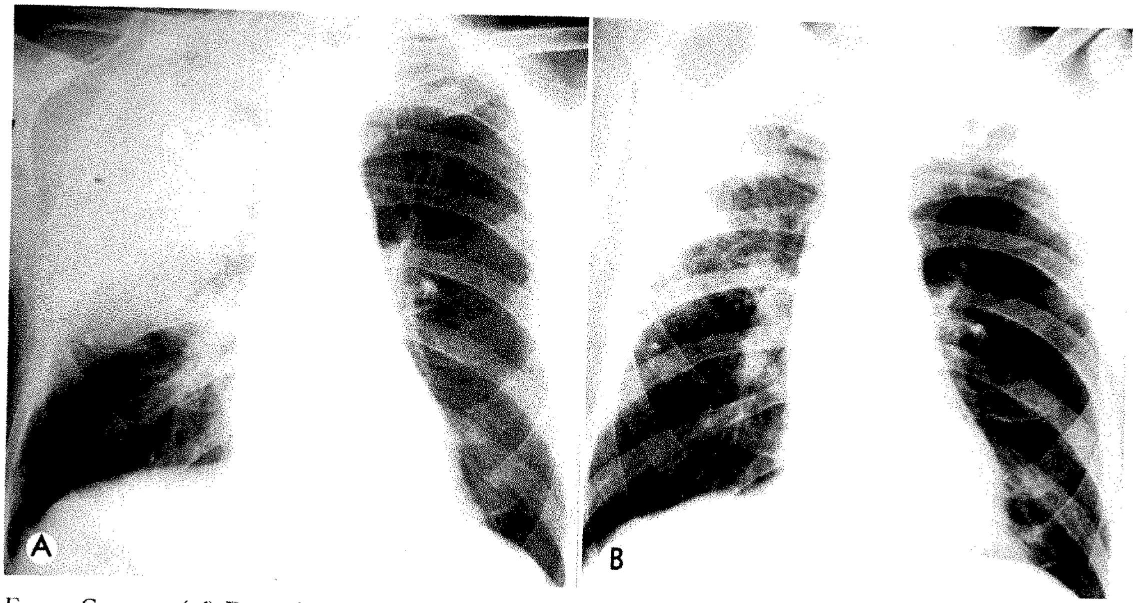

FIG. 7. Case VII. (*A*) December 7, 1961. Dense and homogeneous oval consolidation in the right upper lobe. The medial peripheral portion of the lobe is uninvolved. (*B*) January 22, 1962. The consolidation has resolved.

to show any intrabronchial obstructing lesions. Repeated cytologic studies were negative. The consolidation finally resolved after 6 weeks of vigorous achromycin therapy (Fig. 7*B*).

Case viii. C. S., a 30 year old Negro male, was admitted complaining of chest pain and weight loss of several weeks' duration and hemoptysis for 1 week. His chest roentgenogram showed an oval-shaped mass in the right lower lung field which had sharp borders (Fig. 8*A*). The roentgenographic appearance suggested a tumor mass and the "mass" remained completely unchanged for several weeks despite vigorous antibiotic therapy. Cytologic studies of the sputum were negative. This was also a pneumonic consolidation, localized mainly to the posterior basal segment of the right lower lobe with probably incipient extension into the lateral and medial basal segments. Figure 8*B* shows complete resolution after 10 weeks of antibiotic therapy.

Comment. The patients in this group presented with clinical histories, which did not suggest acute disease or were not specific. In Cases v and vi the consolidations on the admission chest roentgenograms simulated tumors very closely. We assume that in Case vii the consolidation must have spread centrifugally from one central focus and simply did not yet reach the "medial periphery" of the lobe at the time of the initial chest roentgenogram (see Discussion). Case viii was of particular interest because this was a young man and the pneumonic consolidation barely spread beyond one segment. But the oval shape and the sharp borders could not easily be explained by the traditional concepts of pneumonitis.

DISCUSSION

The incidence of bronchogenic carcinoma increased in the past two decades. Parallel with this increase, bronchogenic carcinomas are now diagnosed earlier roentgenologically, partly because the indirect signs of intrabronchial neoplasms have been learned[1,2,7,8] and partly because pulmonary masses are suspected of being malignant earlier than before.[3,5] However, pulmonary masses are not always carcinomas. As we illustrated, certain pneumonic consolidations may imitate bronchogenic carcinomas. This can be explained with the help of a new concept of the pathogenesis of pneumonic consolidations:[4] In the beginning the infection is confined to one bronchopulmonary segment because the infected fluid sinks into the most dependent bronchus. This infected fluid provokes an inflammatory exudate and eventual con-

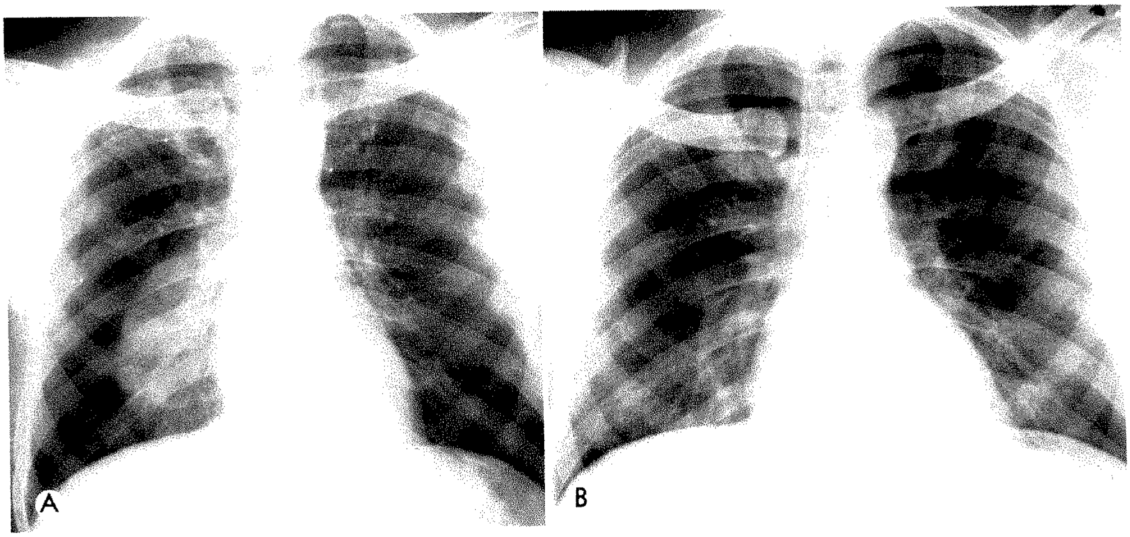

Fig. 8. Case viii. (*A*) January 9, 1962. Sharply demarcated oval consolidation, localized mainly to the posterior basal segment, with incipient extension into the medial and lateral segments. (*B*) March 21, 1962. The consolidation has resolved.

solidation. Previously it was thought that the consolidation had to involve the entire segment and practically fill the segmental bronchus before some exudate would spill over into another segmental bronchus and the consolidation of the next segment commenced. Fraser and Wortzman[4] showed that this is not always the case. The inflammatory exudate crosses from one alveolus to the next through the pores of Kohn, which are special interalveolar communications. The inflammatory exudate crosses from one segment to another with ease since there are no barriers between the segments similar to those between the lobes. Thus, the inflammation spreads in a centrifugal fashion and its advancing front is sharply demarcated from the unaffected lung parenchyma. Klebsiella, pneumococcal and primary tuberculous pneumonias tend to spread in this fashion more often than staphylococcal and streptococcal pneumonias.

We believe, that this above described mechanism is primarily responsible for the oval shape and multisegmental distribution of the pneumonias in the cases we presented. Undoubtedly, the virulence of the infecting organisms, the resistance of the host and the antibiotics do affect the extent and distribution of pneumonic consolidations and also contribute to the appearance of the unusual forms of the disease.[6]

SUMMARY

We have presented 7 cases of pneumonia, some of which were initially diagnosed as neoplasms. Certain pneumonic consolidations may originate from one focus and spread centrifugally from alveolus to alveolus, crossing into adjacent segments before completely involving the original segment itself. This mechanism is primarily responsible for the round or oval shape, sharp demarcation and multisegmental distribution of these consolidations. While the clinical history is often—though not always—helpful, in many cases these consolidations are indistinguishable from pulmonary neoplasms on the basis of the initial chest roentgenogram.

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THE NATURE AND TREATMENT OF DESMOID TUMORS*

By DAVID BENNINGHOFF, M.D.,† *and* ROBERT ROBBINS, M.D.‡
BROOKLYN, NEW YORK AND PHILADELPHIA, PENNSYLVANIA

A DESMOID is a nonencapsulated, locally invasive tumor which occurs in muscle or fascia and which does not metastasize. Stout[15] has classified the desmoid tumor with the fibromatoses, a group of benign tumors formed by proliferation of fibroblastic tissue (Table I). The desmoid is an uncommon tumor. In the largest reported series of fibrous tissue neoplasms, only 19 cases were seen over a 45 year period.[15] In another survey covering a period of 23 years, only 19 desmoid tumors were found among 40,000 neoplasms of all types.[12]

CLINICAL CHARACTERISTICS OF THE DESMOID TUMOR

The desmoid tumor is found in both sexes and may occur at any age. It is most frequent in pregnant or postpartum women involving usually the rectus abdominis muscle. However, it has been found in skeletal muscle at any site.

A specific history of trauma at the precise point of growth is often elicited. The association with pregnancy may also be regarded as traumatic. The usual history is that of a painless, slowly enlarging mass or swelling of soft tissue. It is characteristically deep-seated and its borders are difficult to define. It rarely exceeds 12 cm. in diameter.[15]

PATHOLOGIC FEATURES

The gross tumor is white and has no capsule (Fig. 1). Invasion of muscle was found in all of the 34 cases reviewed by Musgrove and McDonald.[10] The tumor becomes attached to bone and compresses vessels but only muscle is invaded. The vascular elements of the desmoid tumor are scant. Central mucoid changes are found.[18] The following features, as outlined by Gonatas,[4] help to distinguish desmoid tumors from fibromas: (1) deep location and relationship with the musculo-aponeurotic system; (2) diffuse growth and nonencapsulation; and (3) engulfment of muscle fibers.

Microscopically, the tumor is composed of well differentiated fibroblasts within a fibrous stroma. Mitoses are infrequent. Muscle invasion can be seen at the margin of the tumor.[6,10] The fibrous tissue component of the desmoid tumor extends between and around muscle fibers, creating islets of muscle tissue, separated and isolated by tumor (Fig. 2). These isolated muscle fibers are presumed to be finally completely replaced by the tumor. Muscle giant cells may occur in the affected muscle. Clumps of lymphocytes are sometimes seen around muscle fibers adjacent to the infiltrative margins of the tumor. Hemosiderin is not seen in desmoid tumors.

THEORIES OF THE PATHOGENESIS OF DESMOID TUMORS

1. *Hormonal Origin.* Booher and Pack[1] have suggested that desmoid tumors are related to hormonal factors. They cite as evidence for this the frequent association of these tumors with pregnancy and one instance in which tumor regression occurred after irradiation of the ovaries. However, this tumor also occurs in nonpregnant females and in males. Ober and co-workers[11] assayed a resected desmoid tumor but found no increase of estrogens or gonadotropins. The patient of Booher and Pack in

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whom tumor regression followed ovarian irradiation had received radiation therapy to a tumor in the abdominal wall and the ovaries had thus been irradiated incidentally. Hence, regression of the tumor could have been due to direct effect of the radiation upon the tumor.

2. *Origin in a Hematoma.* A history of trauma is obtained in approximately one-half of the patients in whom desmoid tumors are not associated with pregnancy. It has been postulated that a traumatic hematoma may form a nidus for the development of a desmoid. However, microscopic study of desmoid tumors has revealed no hemosiderin content.[6,10]

3. *Origin in an Abnormal Reaction to Injury.* If a hematoma is excluded, is there any other clue to pathogenesis based on reaction to injury? It has been noted that muscle tissue is invariably involved by desmoid tumors. It is possible that contused muscle cells rupture, releasing sarcoplasm into the extracellular space. Could the desmoid tumor be the result of an altered or improper response to this injury? The desmoid tumor might represent a non-self-limiting fibroblastic reaction to injured muscle. It has been postulated that Hashimoto's thyroiditis is an auto-immune disease resulting from auto-antibody to thyroglobulin released into the tissues by rupture of thyroid follicles. A desmoid tumor could represent an auto-immune disease and the aggregates of lymphoid tissue sometimes noted at the margins of the tumor could be involved in the auto-immune process.

Table I

FIBROMATOSES

Fibroma	1,144
Keloids	390
Desmoids	19
Peyronie's disease	0
Palmar and plantar fibromatosis	31
Fibromatosis colli	5
Progressive myositis fibrosa	7
	1,596

Presbyterian Hospital 1906–1951, New York, New York. (After Stout, A. P. AFIP Fasc. 5, 1953.)

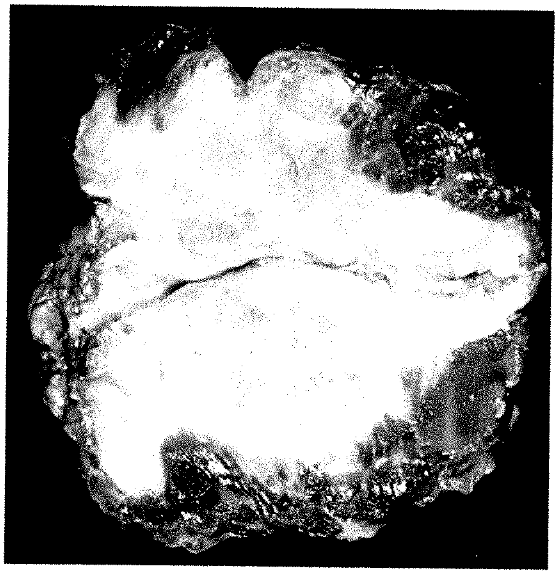

Fig. 1. Cross section of gross specimen of a desmoid tumor. There is no capsule between the tumor and the surrounding muscle.

Objections can be made to the theory of auto-immune pathogenesis. Why should a bulky tumor be produced? Why should normal muscle be invaded and why should an auto-immune process not involve muscles at other sites? Positive data needed to sustain this theory of etiology would include: (1) demonstration of circulating antibody to the patient's muscle tissue; (2) demonstration of gamma globulin at the tumor site. (The fluorescent antibody technique of Coons[2] has been applied by Kaplan[7] to myocardial specimens of rheumatic heart disease patients to demonstrate the presence of gamma globulins.)

One is finally led to the speculation that the effects of local irradiation to the region of a desmoid tumor might be due to an alteration of the immune process rather than to the usual process of cell damage.

TREATMENT

There are few recorded observations of the clinical course of the untreated desmoid tumor. At least 1 case of spontaneous regression has been documented.[17] In a review of juvenile fibromatoses, Stout[16] noted a wide variability in the clinical behavior of these tumors and also their relative benignancy. This type of tumor, in particular, shows regression without treatment in many instances. Stout[15] feels that most desmoid tumors will not recur, even if incompletely excised. On the other hand, it is apparent that in some cases the tumor is aggressive and persistent. Thus, active treatment is required as a general rule.

Surgical excision has been the most frequently employed method of treatment. A number of authors have indicated the re-

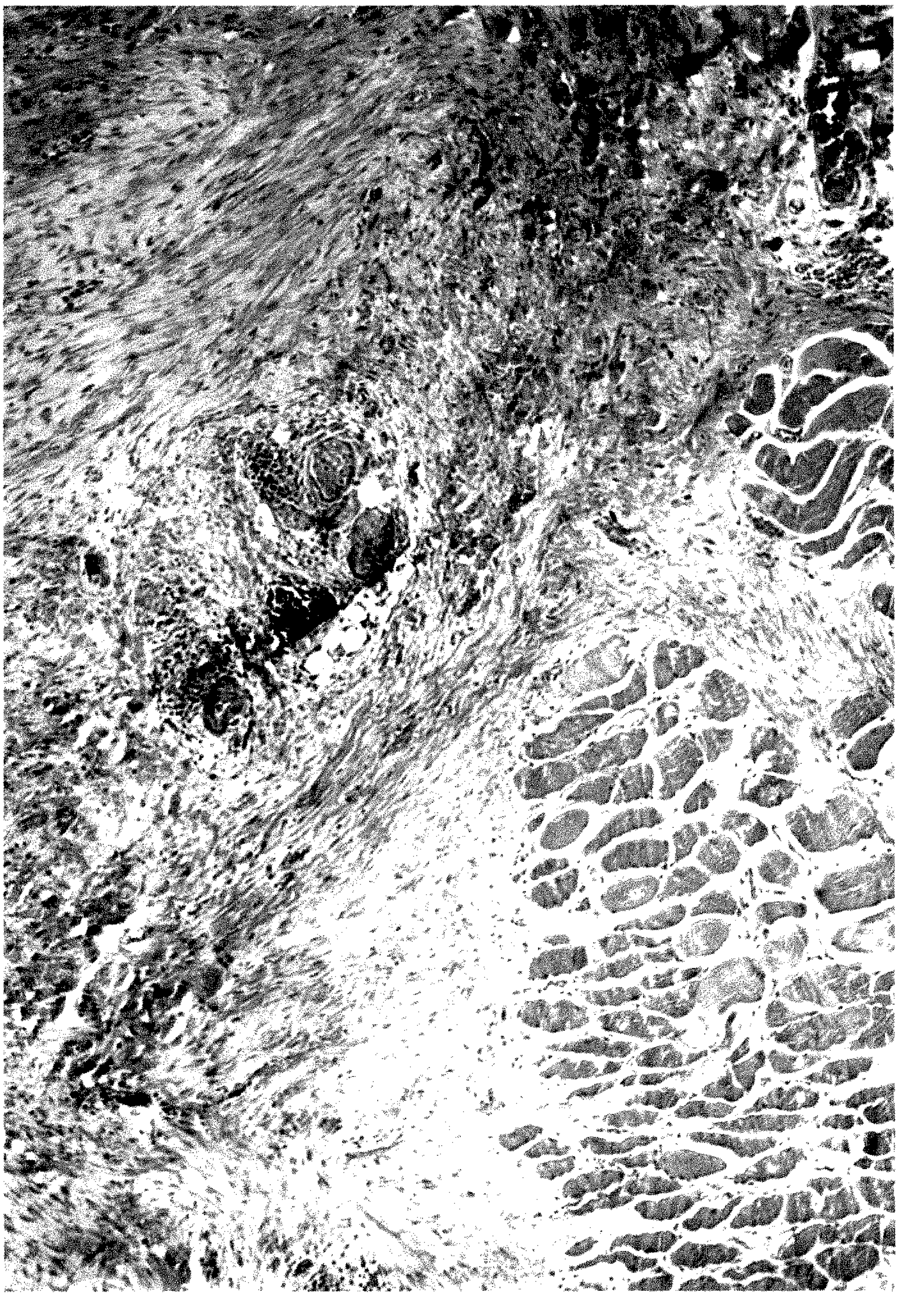

Fig. 2. Microscopic section of a desmoid tumor, again demonstrating the absence of a capsule between the tumor and muscle (H & E ×65).

currence rates following excision. Of 26 cases of desmoid tumors followed for 1 year or more after resection, recurrence was noted in 20.[2] Of 29 cases of extra-abdominal muscle desmoid tumors followed for periods of 2 or more years after treatment, approximately 33 per cent were persistent.[6] Pack and Ehrlich[12] reported 5 recurrences in 18 patients. Mason[8] recorded 4 recurrences in 9 cases of extra-abdominal muscle desmoid tumors.

Because of the high recurrence rate, radical surgical measures are occasionally employed. Hunt *et al.*[6] utilized the following procedures as primary therapy for several of a group of 22 patients with extra-abdominal muscle desmoids: (1) scapulo-thoracic disarticulation in a 24 year old male with a desmoid tumor of the teres major and minor; (2) radical mastectomy in a 36 year old female for a 2×3 cm. desmoid tumor of the pectoralis; and (3) above knee amputation in a 23 year old female for a 5×7×4 cm. desmoid tumor of the popliteal space.

There are varying opinions concerning the value of irradiation in the treatment of desmoid tumors. Ewing[3] observed that desmoid tumors responded slowly but surely to radiation therapy and recommended it for lesions that could not be excised easily.

Musgrove and McDonald[10] were not convinced of the value of irradiation in the management of their series of 34 patients. Nevertheless, their report indicates that 5 of 7 patients who received radiation therapy had no recurrence.

Pack and Ehrlich[12] were favorably impressed by the effects of irradiation in their series of 17 patients. Three inoperable cases of desmoid tumors received radiation therapy and all remained free of recurrence for at least 5 years. Of 4 patients receiving radiation therapy for postoperative recurrence of the tumor, a satisfactory response was obtained in 3, the fourth patient had re-excision and also remained well.

Gonatas[4] described 5 patients, 1 of whom developed a desmoid tumor in the chest wall at the site of a thoracoplasty incision. This tumor grew slowly over a period of 4 years and measured 25×22 cm. prior to treatment. With irradiation, the tumor regressed slowly measuring 4×6 cm. after 2 years and remained the same size for an additional period of 12 years up to the time of the report. Gonatas concluded that radiation therapy should be employed in the larger tumors and in those where surgical resection was incomplete. Gunsett and Oberling[5] reported a case of recovery after radium therapy of a desmoid tumor involving the soft tissues of the shoulder.

Since desmoids are "benign" lesions, conservative rather than radical methods of treatment would appear to be justified. The employment of radical surgical procedures is thus open to serious question. Radiation therapy should be given for tumors which are not completely extirpated by surgery, for recurrence, and for inoperable cases.

Plantar fibromatosis is a much less serious clinical problem. In general, smaller doses of irradiation are required for this lesion than are needed with desmoid tumors. As indicated above, plantar fibromatosis tends to regress without any treatment.

Medical treatment is confined to the use of prednisone in high doses over a prolonged period. Panos and Poth[13] report successful treatment with prednisone of a second recurrence of a desmoid tumor in a 22 month old female. Their patient was originally operated upon for a desmoid tumor of the lower right rectus muscle. A 4×6 cm. recurrent mass was noted in the healed surgical incision 5 months later. Wide re-excision was performed, but residual tumor was left attached to the symphysis pubis. Three months later a firm nodule 1.5×1.0 cm. was still present in the scar area. Prednisone therapy was instituted and the authors describe the response as " . . . spectacular. Within three weeks the nodule had disappeared and the lower abdominal wall . . . softened perceptibly . . . becoming more pliable until . . . there was no thickening or induration." No evidence of tumor was found when the child was examined more than 5 years following institution of prednisone therapy.[14]

Thus prednisone therapy should be considered in instances where surgical excision followed by irradiation has not eradicated the tumor. However, if the hazards of cortisone therapy are weighed against the particular problems which a given desmoid tumor presents when management by other means has failed, the risks would appear to be negligible. Mosbech[9] has quantitated the risk of fatal complications due to treatment with cortisone. He reviewed the Danish vital statistics for the 5 year period, 1955–1959 and found that 38 patients died of direct complications of cortisone therapy during that period. This represented an annual mortality, attributable to this drug, of between 1 and 2 deaths per million for the entire population of that country.

TREATMENT OF CASES PRESENTED IN THIS REPORT

This report includes 4 patients with desmoid tumors and 2 with plantar fibromatosis. Surgical excision combined with postoperative irradiation was used in the 4 patients with desmoid tumors; one of these was given prednisone as adjuvant therapy. Three of the 4 patients are free of disease a minimum of 5 years after treatment; the fourth patient (Case I) has been free of recurrence for 2 years. The 2 patients with plantar fibromatosis were treated with surgical excision followed by irradiation, the latter given in smaller doses than for the desmoid tumor.

REPORT OF CASES

Case I. E.W., a 21 year old nurse, struck her left inguinal area on a stretcher in June, 1960. Eight months later a 10×12 cm. mass with ill-defined borders was noted in the abdominal wall in the area of the injury. The mass appeared to be attached to the inner surface of the symphysis pubis and involved the inguinal ligament laterally. The left lower extremity was edematous.

Biopsy of the mass revealed a desmoid tumor. An operation was performed in February, 1961 by Dr. Irving Enquist at the Kings County Hospital Center. Most of the tumor was removed but in order to preserve normal structures approximately 15 per cent of the total tumor mass was left *in situ.*

Three weeks after operation external irradiation was given to the area of resection: 3,000 r tumor dose in 3 weeks via a 10×10 cm. field. The patient did well for a period of 3 months when leg edema became noticeably increased and a hard 6×8 cm. mass was palpated just medial to the anterior superior iliac spine. This was regarded as a recurrence, lateral to the irradiated volume. Following 2 weeks of therapy with prednisone, given in daily doses of 80 mg., the mass was no longer palpable and the leg edema had diminished. Prednisone in decreasing dosage was continued until December, 1961.

There is no evidence of tumor in this patient 2 years after therapy of the recurrent tumor with prednisone.

Case II. M.C., 37 years old, was seen at Temple Hospital in 1955 with a desmoid tumor of the neck and mediastinum. She was explored by Dr. W. Emory Burnett, who removed the bulk of a desmoid tumor which infiltrated the neck muscles, and also extended posteriorly to attach to the lateral masses of the cervical vertebrae and inferiorly to involve the mediastinum.

Eight months later the patient was readmitted to the hospital because of dyspnea secondary to tracheal compression by the desmoid tumor in the mediastinum. Radiation therapy to the mediastinum was instituted and a tumor dose of 3,000 r in 4 weeks was delivered. The tumor regressed very slowly, and when seen in March of 1960 the patient was essentially normal.

Case III. W.N., a 9 year old boy, was seen originally in 1953 for a mass in the right popliteal space (size not stated). The mass was excised and proved to be a desmoid tumor on pathologic examination. It recurred within 8 months and a second resection was done, at which time the tumor was found to be adherent to the popliteal artery; in order to avoid resection of the artery, tumor tissue was left behind. Postoperative radiation therapy was given, 2,000 r in 3 weeks. The boy is without recurrence 7 years later.

Case IV. S.C., a 36 year old male, was seen in 1956, 3 months after an injury to the right arm.

A hard mass, 6 cm. in diameter, was palpated in the mid-portion of the biceps muscle. The mass was resected and found to be a desmoid tumor. In March 1957, 5 months after the initial resection, local recurrence was noted and a second resection was done. This was followed by radiation therapy, 4,000 r in 4 weeks. This patient was well, without recurrence 5 years after initial treatment.

Case v. B.S., a 12 year old boy, was seen in March, 1957, for a 2 cm. firm, painless, subcutaneous mass on the medial aspect of the plantar surface of the left foot. This was excised. A recurrence, 1 cm. in diameter, was excised in August, 1957. In September, 1957 several additional 1 cm. nodules were found in the plantar fascia. These were also excised and proved to be plantar fibromatosis. A dose of 1,500 r in 10 days was given to the plantar surface of the foot. No recurrence was found in 1961, 4 years after surgery and irradiation.

Case vi. A.S., a 59 year old female, had noted hard, tender lumps on the soles of both feet for many years. In 1953 these were excised; they recurred and were re-excised in 1957. Histologic examinations showed plantar fibromatosis. Postoperatively, 600 r was given to the soles of both feet in 2 weeks. In July, 1958 an additional 1,300 r was given to a recurrence on the right sole. The anterior and posterior plantar surfaces of the left foot were treated separately with 600 r for palpable recurrence in 1959, and 1961. The right foot has been free of recurrence for 3 years.

SUMMARY

The desmoid tumor and its natural history are described. Four patients with desmoid tumors and 2 with plantar fibromatosis treated by a combination of surgery and irradiation, and prednisone additionally in 1 case, are reported.

Since the desmoid tumor is benign, conservative management is suggested.

The pathogenesis of the tumor is discussed, particularly the possibility that it represents an altered response to injury.

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CALCIFICATIONS IN INTRA-ABDOMINAL AND RETROPERITONEAL METASTASES[*]

REVIEW OF THE ROENTGENOGRAPHIC FEATURES

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THE roentgenographic demonstration of calcification in certain primary intra-abdominal[7,16,29,30,39,40,42,47,64,77] and retroperitoneal[5,8,18,25,32,44,54–56,68] malignant tumors is well documented. That calcification in metastatic tumors has been seen on abdominal roentgenograms is less widely known. The purpose of this communication is to review the reported roentgenographic features of calcified intra-abdominal and retroperitoneal metastases and to present an illustrative case.

Certain explanations should be made regarding the selection of cases for this study. Lymphomas were excluded in the belief that the lesions are not truly metastatic.[*] Neuroblastomas were omitted because the roentgenologic detection of calcium in this tumor and its satellite lesions has been well documented previously.[32,44] A unique case of pseudomyxoma peritonei with numerous calcified intra-abdominal cysts[49] was included because this type of tumor, although histologically benign, is clinically malignant.

No attempt was made to correlate the appearance of calcification in metastases with the use of chemotherapy or radiation therapy, because information on this point often was lacking or unclear in the material surveyed. For the same reason the presence or absence of histologically detectable calcifications in the primary lesions was not tabulated in every case. Finally, the term "metastasis" as used in this report is intended to mean extension, local recurrence or distant spread of the primary tumor.

REPORT OF CASE

A 49 year old white man was first seen in October, 1958, because of painless, gross hematuria. The past medical history was noncontributory. Physical examination revealed a healthy appearing man in whom no abnormal physical findings were detected. The urinalysis showed microscopic hematuria. Cystoscopy furnished no evidence of neoplasm. Abdominal roentgenograms disclosed no abnormality. Intravenous urograms and retrograde pyelograms demonstrated distortion of the right calyceal system. The clinical diagnosis was tumor of the right kidney. A right nephrectomy was performed on October 22, 1958, at which time a mass 5.0 cm. in diameter was found in the lower pole of the involved kidney. No regional metastases were seen. Histologically, the specimen showed renal cell carcinoma with tumor thrombus in the renal vein.

The patient remained well until 28 months after nephrectomy when he noted pain in the left groin and lumps in the left supraclavicular space and in the area of the right pectoralis major muscle. The right pectoral mass was excised and found to be an undifferentiated carcinoma compatible with origin from the kidney.

On July 10, 1961, he entered the University of Texas M. D. Anderson Hospital and Tumor Institute. Physical examination on admission revealed hard masses in the left submandibular, left supraclavicular and right pectoral muscle areas. Abdominal roentgenograms on July 14, 1961, demonstrated a calcified mass in the left iliac fossa and osteoblastic reaction in the lateral aspect of the left iliac bone (Fig. 1*A*). Subsequent roentgenograms on September 17,

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[*] Roentgenographically demonstrable calcification in lymphomatous tumors is rare, having been reported but once as a spontaneous phenomenon[10] and only a few times following specific therapy.[20]

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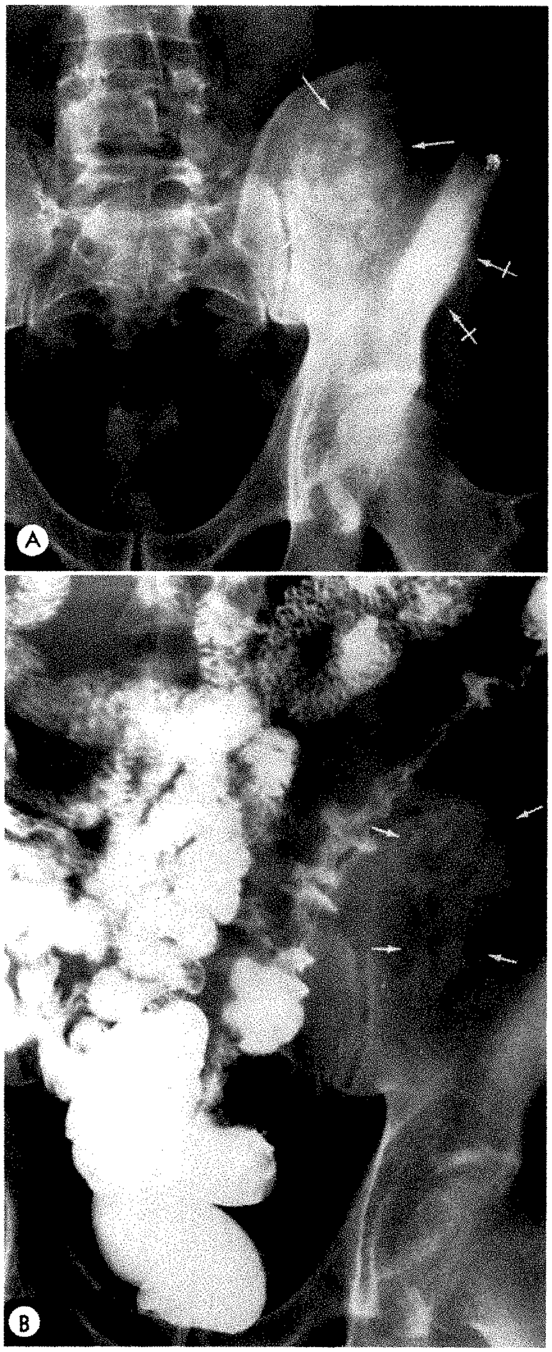

Fig. 1. (*A*) Calcification in metastasis from carcinoma of the left kidney. → point to calcification in soft tissue metastasis in left iliac fossa. +→ point to osteoblastic metastasis in ilium. (*B*) Barium enema study showing medial displacement of descending colon by the calcified metastasis.

1961, demonstrated enlargement of the calcified area and no involvement of the urinary tract. The descending colon showed no evidence of intrinsic disease but was displaced anteromedially by the mass (Fig. 1*B*). Many roentgenograms of the chest were normal. Three days after admission, specific antitumor therapy was begun for the first time. This consisted of various chemotherapeutic agents (alpha-sarcin, carzolamide, phenylalanine mustard and vinblastine sulfate) followed 2 months later by irradiation to the left iliac fossa. The patient's hospital course was characterized by progressive cachexia, left groin pain, enlargement of superficial metastases and the development of anemia and ascites. He died on October 10, 1961.

At autopsy, metastases were widespread throughout the body. The histologic appearance of these metastases was similar to that of the original renal carcinoma. Of particular interest was the mass which had been seen roentgenographically in the left iliac area (Fig. 1, *A* and *B*). It measured 20×12×10 cm. and weighed 2,000 gm. It extended from the level of the fifth lumbar vertebra to the obturator fossa medially and to Poupart's ligament laterally. Histologically, this metastasis showed considerable fibroblastic reaction and necrosis. In the areas of necrosis, there was calcification with minimal bone spicule formation.

COMMENT

A review of the English language medical literature and many pertinent foreign reports revealed 56 cases in which roentgen examination demonstrated calcifications in intra-abdominal or retroperitoneal metastases (Table I). Except for one patient with carcinoma of the colon[77] and some of the patients with ovarian cancer, the calcifications in the cases analyzed for this study were seen in metastases but not in the primary tumor.

Calcification in abdominal metastases has been reported most frequently in papillary cystadenocarcinoma of the ovary (Table II). The characteristic type of calcification in this tumor is the psammoma body. Psammoma bodies, sometimes called calcospherites and microliths, are non-

TABLE I

CALCIFICATIONS IN INTRA-ABDOMINAL AND RETROPERITONEAL METASTASES

Site of Metastasis	Ref. No.	Primary Tumor		Roentgenographic Features of Calcifications	Remarks
		Site	Histologic Type		
Liver	9	Sigmoid	Adenocarcinoma	Multiple particles arranged in a ring	
	1	Sigmoid	Adenocarcinoma	Granular	Metastases showed mucus-secreting adenocarcinoma
	74	Sigmoid	Carcinoma	Feathery, faint	Gross hepatic metastases seen at celiotomy. No biopsy taken. Primary tumor with regional metastases removed $2\frac{1}{2}$ years previously
	74	Sigmoid	Carcinoma	Small particles in region of right lobe	Calcium deposition in center of tumor nodules and in portions of necrotic liver tissue
	28	Sigmoid	Adenocarcinoma	Fine, granular, diffuse	Calcifications increased in number during a 10 month period, coalescing but remaining fine and granular
	22	Sigmoid	Adenocarcinoma	Fine, confluent particles	Calcifications enlarged during a 3 month period
	31	Sigmoid	Carcinoma	Two groups of punctate densities; one in left lobe, one in right lobe	
	69	Rectosigmoid	Colloid carcinoma	Innumerable, small, punctate shadows in right lobe	
	31	Colon (ascending)	Carcinoma	Innumerable punctate particles covering an area 3 inches wide in the right lobe	
	1	Colon (ascending)	Adenocarcinoma	Stippled, dense and coalescing	
	74	Colon?	Adenocarcinoma	Small, faint, punctate	Origin of primary tumor not proved. Presumed to be colon on basis of clinical history and histologic evidence of mucous glands in hepatic metastases
	60	Rectum	Adenocarcinoma	Extensive throughout right lobe	
	60	Bile Duct	Carcinoma	Mottled in clumps	
	38	Stomach	Adenocarcinoma	Large, irregular, nodular mass in right lobe	*Metastases were mucinous. Authors refer to other reports in the foreign medical literature on single cases of calcified hepatic metastases from tumors originating in the gallbladder, pancreas, stomach and breast
	36	Bronchus	Adenoma	Amorphous densities	Calcifications appeared following radiation therapy to liver area
	53	Breast	Carcinoma (ductal)	Numerous, variable in size and dense	
	37	Eye	Malignant melanoma	Multiple nodular areas up to 10 cm. in diameter; some dense throughout; others with peripheral rim only	

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* Psammoma bodies identified histologically in primary and/or metastatic lesions.

Table I—(*Continued*)

Site of Metastasis	Ref. No.	Primary Tumor		Roentgenographic Features of Calcifications	Remarks
		Site	Histologic Type		
	60	Salivary gland	Myxochondrocarcinoma	Diffuse, irregular throughout most of right lobe	Patient had recurrent salivary gland cancer. Needle biopsy of liver showed adenocarcinoma compatible with salivary gland origin
Spleen	75	Stomach	Carcinoma	Irregular, mottled	
	45	Ovary	Pseudomucinous cystadenocarcinoma	Curvilinear	
Left Adrenal Area	66	Ovary	Papillary cystadenocarcinoma	"Apple-sized," ring-shaped	
Upper Abdominal Area	12	Ovary	Leiomyosarcoma	Dense, punctate and mulberry-like	Calcified and noncalcified metastases in both adrenal glands and surrounding lymph nodes. Primary tumor was calcified
Retro-peritoneal Area	20	Testis	Embryonal carcinoma	Coarse, irregular granules; small plaques	Calcifications were noted 2 months after chemotherapy
	20	Ovary	Dysgerminoma	Punctate; 1 cm. areas of confluence	Calcifications were noted 5 weeks after Co^{60} radiation therapy
Presacral Area	21	Rectum	Adenocarcinoma	"Small ossifying growth"	Metastasis was ossified
	69	Rectosigmoid	Colloid carcinoma	Many small shadows anterior to the second, third and fourth sacral segments	Calcifications were presumed to be in recurrent carcinoma. Primary lesion had been removed 8 years previously and recurrence in urinary bladder was proved histologically
Pelvic Area	63	Rectum	Adenocarcinoma	Dense, lobulated single mass	Metastasis was ossified
	35	Ovary	Papillary cystadenocarcinoma	Hazy, amorphous; scattered obliquely throughout pelvis	*
	20	Cervix	Carcinoma	Coarse, granular	Calcifications were noted 16 months after radium and roentgen-ray therapy
	35	Ovary	Papillary cystadenocarcinoma	Minute, near left uretero-pelvic junction	*
Right Lower Quadrant	13	Ovary	Papillary cystadenocarcinoma	Fine, granular	* Calcifications simulated feces
	13	Ovary	Papillary cystadenocarcinoma	Mottled, fine	*
Right Upper Quadrant	77	Colon (ascending)	Mucinous adenocarcinoma	Fine, irregular and mottled	The primary tumor and one regional lymph node were calcified. The calcifications were mistaken for feces
Left Iliac Fossa		Kidney	Carcinoma	Cluster of irregular and ill-defined densities measuring 5 cm. in maximum diameter	This is the case described in this report
Distal Colon	11	Ovary	Papillary adenocarcinoma	Hazy	* Calcifications simulated barium and feces
Widespread	35	Ovary	Papillary cystadenocarcinoma	Numerous large (up to 15×5.5 cm.) and small areas	*
	35	Ovary	Papillary cystadenocarcinoma	Multiple large masses (up to 6×19 cm.)	*

TABLE I—(*Continued*)

Site of Metastasis	Ref. No.	Primary Tumor		Roentgenographic Features of Calcifications	Remarks
		Site	Histologic Type		
Widespread	35	Ovary?	Papillary cystadenocarcinoma?	Multiple, large, hazy amorphous areas	Roentgen findings characteristic of papillary cystadenocarcinoma of ovary. Histologic proof not obtained. "Roentgen diagnosis confirmed by peritoneoscopy"
	58	Ovary	Papillary cystadenocarcinoma	Multiple rounded densities in area of spleen, liver and pelvis. Large, dense irregular mass in left iliac fossa	* Patient died 18 years after histologic diagnosis was made and 9 years after calcifications were first seen on the abdominal roentgenogram
	57	Ovary	Psammo-adenocarcinoma	Rounded densities, especially prominent in the subhepatic region, varying in size from "pin head" to "prune," and extending to right iliac fossa	*
	43	Ovary	Papillary cystadenocarcinoma	Irregular and of varying density	* Calcifications extended to above the right diaphragm and into the right lung
	59	Ovary	"Psammocarcinoma"	Variable sized with poorly defined borders	
	17	Ovary	Papillary cystadenocarcinoma	Numerous, small densities of varying size	* Calcifications decreased following radiation therapy
	17	Ovary	Papillary cystadenocarcinoma	Densities primarily in left part of abdomen and region of right gutter	*
	72	Ovary	Papillary adenocarcinoma	Hazy, speckled densities, especially in right hypochondrium. "Banana-sized" area in left side of pelvis	* Calcifications first noted one-half year after roentgen therapy
	72	Ovary	Papillary cystadenocarcinoma	Faint, "apple-sized" areas in both adnexal regions; 5-6 cm. long, band-like area in mid pelvis	* Calcifications first noted following roentgen therapy
	23	Ovary	Papillary cystadenocarcinoma	Hazy, granular; more dense and larger zones in mid pelvic and right adrenal areas	* See Fig. 2, *A*, *B* and *C* in this report
	50	Ovary	Carcinoma	Variable sized, rounded, dense nodules with fairly regular borders grouped especially in left hypochondrium, sigmoid, splenic and hepatic regions	* This same case is described in 2 other reports[51,52]
	76	Ovary	Papillary cystadenocarcinoma	Homogeneous hazy area in pelvis consisting of innumerable, discrete, punctate deposits. Conglomerate, punctate densities in both upper quadrants	*
	13	Ovary	Papillary cystadenocarcinoma	Densities filled entire pelvis and most of abdomen. Looked like barium both inside the gut and free in the peritoneal cavity	* One calcified metastatic lesion seen in anterior chest wall
	13	Ovary	Papillary cystadenocarcinoma	Faint, granular densities in right mid abdomen, left upper quadrant and possibly in a large mid-abdominal mass	* Calcification initially taken for feces

Table I—(*Continued*)

Site of Metastasis	Ref. No.	Primary Tumor		Roentgenographic Features of Calcifications	Remarks
		Site	Histologic Type		
Widespread	2	Ovary?	Papillary cystadenocarcinoma?	Numerous, nodular, confluent densities of various sizes, primarily in left hypochondrium	Authors imply that calcifications were widespread. Primary tumor believed to be ovarian on basis of pelvic mass and histologic appearance of ascitic fluid
	70	Ovary	Papillary serous cystadenoma	Ring-shaped; up to "apple" in size	Cause of calcifications not proved. Authors assumed that the ovarian tumor had undergone malignant degeneration with spread.
	67	Ovary	Osteogenic sarcoma	Not described and roentgenograms not published	Abdominal roentgenogram reported to show calcifications scattered throughout the lower part of the abdomen
	62	Ovary	Round-cell scirrhous carcinoma	Multiple, dense, rounded, variable-sized	Liver studded with calcified metastases
	19	Ovary	Cystadenocarcinoma	Extensive, mottled, large and small	Similar calcifications were seen in the lungs
	49	Not stated	Pseudomyxoma peritonei	Diffuse, annular	Origin of primary tumor not mentioned in this male patient

birefringent, laminated, roughly spheric, calcific particles which measure 5 to 100 μ in diameter. They are found occasionally in a variety of tissues[14,24,34,65] but are common only in the ovary,[3,34] the central nervous system[15,33,48] and carcinoma of the thyroid.[3,33,61,71] When they occur in a carcinoma, the term psammocarcinoma often is used.

The roentgenographic characteristics of psammous calcification in papillary cystadenocarcinoma of the ovary depend upon the size of the neoplastic masses, the extent of metastases and the concentration of psammoma bodies in the lesions.[23] The resulting shadows sometimes are strikingly opaque. More commonly, they appear indefinite and cloud-like on the roentgenograms, only slightly denser than soft tissues. In fact, psammous calcification may simulate feces[11,13] or be mistaken for a fine coating of barium adherent to the mucosa of the bowel.[11,13,35] Often the calcific deposits coalesce to form a mottled or finely nodular appearance (Fig. 2, *A*, *B* and *C*). Roentgenographically detectable psammous calcifications may be confined to the primary tumor or its immediate surrounding structures,[35] or to just one abdominal metastasis.[11] However, when they are spread widely about the abdomen, their density and distribution as seen on the plain abdominal roentgenogram are characteristic and should permit the diagnosis of metastatic psammocarcinoma of the ovary.[13,17,23,35,43,50,57–59,72,76] Of the few other tumors reported which showed widespread calcifications on the plain abdominal roentgenogram, all but one[49] originated in the ovary, and the pattern of calcification in their metastases was variable.[2,19,62,67,70]

In the differential diagnosis of widespread abdominal calcifications, ovarian tumor should be given primary consideration because few other disorders produce such a picture. Careful study should prevent any diagnostic confusion with opaque material scattered along the gut,[13,17] small phleboliths occurring in hemangiomatosis of the mesentery, small intestines or omentum,[69] or the diffuse peritoneal calcifications resulting from healed tuberculosis,[6,27,46,73] oil granuloma[4] or echinococcosis.[26]

In the differential diagnosis of localized

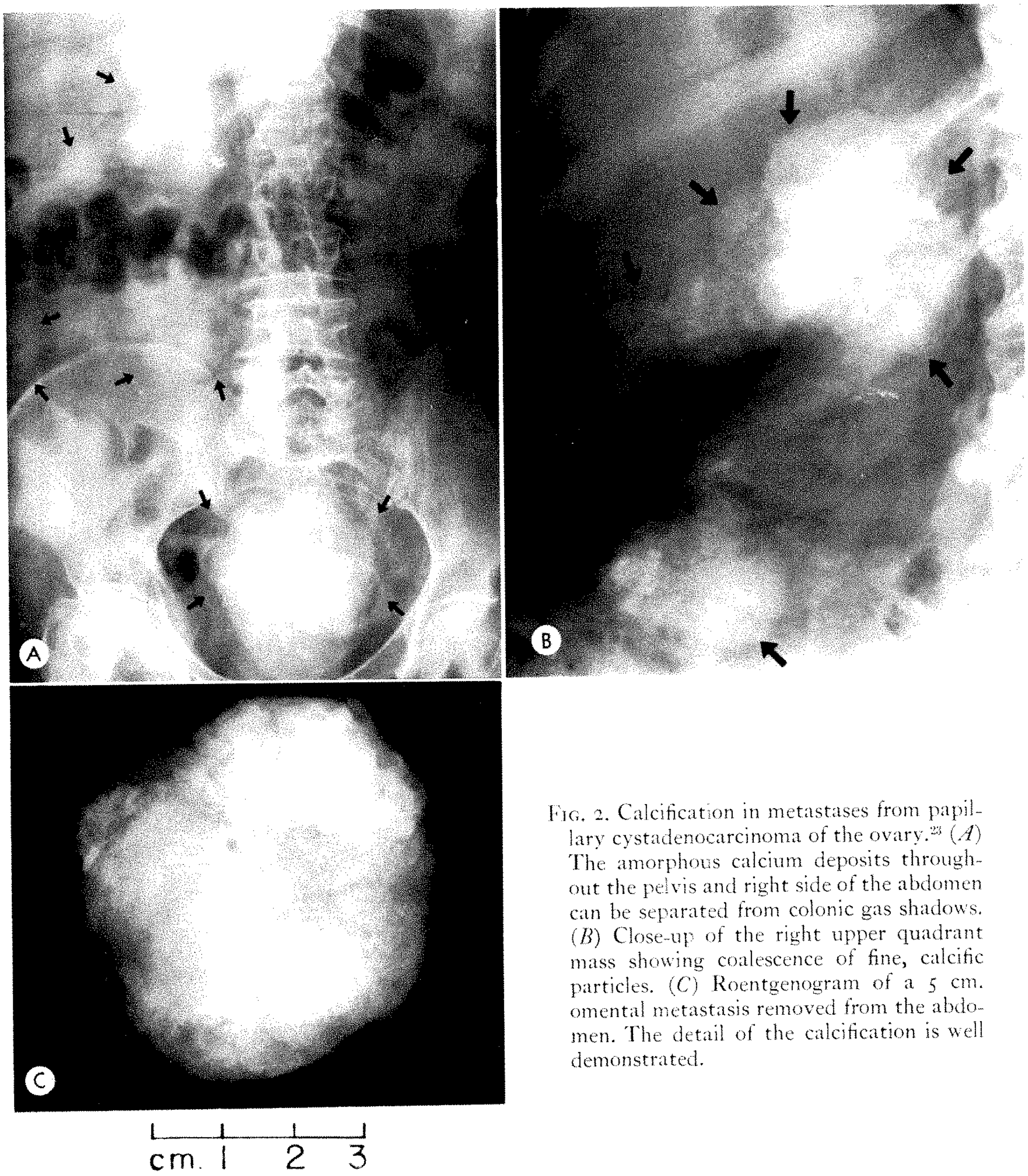

Fig. 2. Calcification in metastases from papillary cystadenocarcinoma of the ovary.[23] (*A*) The amorphous calcium deposits throughout the pelvis and right side of the abdomen can be separated from colonic gas shadows. (*B*) Close-up of the right upper quadrant mass showing coalescence of fine, calcific particles. (*C*) Roentgenogram of a 5 cm. omental metastasis removed from the abdomen. The detail of the calcification is well demonstrated.

calcifications within the abdomen, the possibilities are more numerous and the correct roentgenologic interpretation is more difficult. These various diagnostic considerations have been reviewed in detail by McAfee and Donner.[41] The point we wish to emphasize is that localized intra-abdominal calcification occasionally may represent metastatic tumor. The locus of the calcification may offer some clue to the origin of a calcified metastasis. Hazy or stippled calcifications localized to the area of the liver should suggest hepatic metastases from adenocarcinoma of the colon, especially the sigmoid[1,22,28,31,69,74] (Table II); however, similar calcifications in the right upper quadrant occurring in a primary carcinoma of the ascending colon

Table II

CASES OF CALCIFIED INTRA-ABDOMINAL AND RETROPERITONEAL METASTASES TABULATED ACCORDING TO SITE OF PRIMARY TUMOR

Site of Calcified Metastases	No. of Cases	Primary Tumor		
		Ovary	Colon	Other
Widespread	22	21	—	1
Localized	35			
Hepatic	18	—	12	6
Nonhepatic	17	9	4	4
Total	57 (100%)	30 (53%)	16 (28%)	11* (19%)

* It is noteworthy that in these 11 cases, there were 10 different primary sites, the stomach being the primary site in 2 instances.

have been noted in 2 patients.[77] A small zone of hazy, stippled calcification confined to the pelvic area or lower part of the abdomen is likely to be caused by a psammocarcinoma of the ovary[35] or one of its metastases,[11] but a similar roentgenographic picture may result from a benign papillary cystadenoma of the ovary[35] or a primary carcinoma of the rectum[56] or colon.[40] As shown in Table I, metastases containing calcium may be confined to other relatively small areas of the abdomen, but in such instances, their roentgenographic appearance is nonspecific. This point is illustrated by the case reported here in which there was much uncertainty regarding the nature of the calcified mass in the left iliac fossa. Indeed, no other case of roentgenographically detected calcified abdominal metastasis from renal cell carcinoma was found in our review of the medical literature.

The pathogenesis of calcification in metastases is poorly understood. Possible etiologic factors such as hemorrhage, necrosis and an elevated serum calcium concentration often cannot be demonstrated, particularly in the cases of psammocarcinoma. It should be pointed out that most of the primary carcinomas of the gastrointestinal tract containing roentgenographically demonstrable calcium have been mucinous in type.[64] In such cases the calcium has been found predominantly within accummulations of mucin. However, in the calcifying secondary tumors reviewed here, the histologic descriptions rarely included mention of mucous glands.[1,38,74]

SUMMARY

An analysis of the roentgenographic features of 57 cases of calcified intra-abdominal and retroperitoneal metastases permits the following conclusions:

1. Widespread intra-abdominal calcifications should suggest metastatic ovarian tumor, particularly psammocarcinoma.
2. Hazy or stippled calcifications confined to the region of the liver should suggest hepatic metastases from adenocarcinoma of the colon, especially the sigmoid.

A case of calcified intra-abdominal metastasis detected by roentgenologic examination is presented. The primary lesion was a renal cell carcinoma.

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ADDENDUM

More recently, Karras *et al.*[79] and Miele and Edmonds[80] reported on a total of 7 additional patients with finely granular intrahepatic calcifications representing metastases from carcinomas arising in various regions of the colon, and Curry and Howland[78] called attention to discrete opacities spread widely throughout the colon of 2 children who nibbled on erasers. These authors found that some abrasive erasers contain significant amounts of barium sulfate and calcium carbonate.

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COBALT 60 THERAPY IN THE MANAGEMENT OF PERINEAL RECURRENCE FROM CARCINOMA OF RECTUM AND COLON*

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RADIATION therapy does not play a major part in the treatment of carcinoma of the rectum and colon today. The emphasis in the literature has been placed on the surgical management of these lesions. That is as it should be since usually surgery offers the only chance of a cure. Henschke[5] in 1959 referred to the number of articles written on the use of radiation therapy in this disease. He noted peaks of interest in the late 1920's and again in the decade between 1935 and 1945, and a marked drop in the number of articles written between 1945 and 1955. He prefaced his presentation by showing surprise that a radiotherapist should be asked to participate in a symposium on colonic and rectal neoplasia. Our review of the literature shows the lack of radiotherapeutic interest noted by Henschke to continue to the present time.

The accepted treatment for carcinoma of the rectum and colon is the abdominoperineal or Miles resection.[8] The reported 5 year survival figures for these lesions vary widely. Welch and Burke,[14] in 1962 found a 57 per cent 5 year survival in their study of 1,800 cases. Shallow *et al.*[11] in 1955 had an over-all survival rate of 33 per cent; Gilchrist[4] in 1962 stated that a 50 per cent 5 year survival rate is to be expected in tumors arising below the peritoneal reflection. Garlock *et al.*[2] found survival figures of 28.3 per cent for ward patients and 56.3 per cent for private patients and Dukes and Bussey[1] reported corrected 5 year survival figures of 57.4 per cent. There is general agreement that the best chance for improvement in survival lies in earlier diagnosis.

Patients in whom the cancer is not eradicated may present at a later date with either local recurrence or distant metastases. The most common symptom of local recurrence is pain, whether the recurrence is in the pelvis, abdomen, vagina or perineum. Although this pain may be very severe, the patient's general condition is often surprisingly good. If the pain can be relieved, he may continue to lead a useful life for many months or years. Although carcinoma of the rectum and colon has been considered to be a radioresistant tumor, it has been our experience that the symptoms due to local recurrence can be palliated very adequately by supervoltage radiation therapy. In this report the value of palliative radiation therapy for the perineal recurrences is considered. The definition of perineal recurrence is limited to those cases in which there is soft tissue implantation of cancer cells in the area between the external genitalia and the coccyx. The lesions of the underlying bony pelvis and sacrum or invasion of the bladder or vagina are not included. Intrapelvic disease is also not included.

The perineum is a fairly common site for recurrence of rectal carcinoma. In the series of Shallow *et al.*[11] 7 per cent of the recurrences were classified as perineal. Williams *et al.*[15] report 28 cases of perineal recurrence in their series of 82 cases treated by supervoltage radiation. Recurrence in the perineum represents a distressing problem to both the patient and his doctors. The patient presents with severe deep boring pain in his perineum and upper thighs. In many cases a foul discharging mass close to or in direct approximation with the surgical perineal scar is present. The situation is such that walking or sitting becomes exceedingly difficult. The pain leads to anorexia and malnutrition and complicates the problem. Although uncomfortable and unable to work, many of these patients have a life expectancy of over 18 months, and palliation therefore becomes imperative.

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CASE MATERIAL

The records were analyzed of all patients treated for carcinoma of the rectum and colon in the Division of Radiotherapy of the Jefferson Medical College Hospital between 1957 and 1962. Of some 60 patients, 13 represented examples of perineal recurrence according to our earlier definition. The other cases include vaginal recurrence, intra-abdominal recurrence at the operative or anastomotic site, local bony invasion and distant metastatic disease. All 13 patients were treated with cobalt 60 beam radiation. Three of the patients received 5-fluorouracil in conjunction with their irradiation; 2 others got this agent at a later date in the course of their disease. Most of the patients were treated with a direct perineal portal. Rotation and opposed portals were used less frequently. A dose of 4,500 to 5,500 r was delivered whenever possible in 4 to 5½ weeks.

There were 3 females and 10 males. The average age was 60 years; the interval between surgery and the recurrence of symptoms in the perineum ranged between 3 and 42 months, with an average of 15 months. Eleven of the 13 patients had Miles abdominoperineal resection; 1 had a colostomy and 1 had a pullthrough procedure.

It is quite difficult to evaluate the results in a disease process such as perineal recurrence. Obviously, the subjective response as well as the objective change in the tumor must be considered. Remington,[9] in his discussion of palliation in recurrent rectal and colonic carcinoma cites four aims which we feel summarize the situation well: (1) relief of pain; (2) prevention or relief of obstruction; (3) prolongation of a useful life; and (4) the providing of moral support. In perineal recurrence the prevention of obstruction is not applicable, but the other 3 criteria provide a useful measure upon which to gauge our results.

In Table I a summary of each patient's course is given. We have set up our own standards to classify the effects of treatment and these are shown in Table II. By these standards, our results are summarized in Table III.

REPORT OF CASES

CASE 1. (This case has been reported previously in detail.[7]) V.F., a 57 year old white female school teacher, underwent a Miles resection for rectal carcinoma in April of 1957. In November of 1958, a 5 cm. nodule was noted in the left buttock and a 2 cm. nodule in the right buttock. These nodules were tender and quite painful. She was treated with Co^{60} beam radiation to a dose of 5,500 r in 29 days through a direct perineal portal. Symptoms were relieved and the masses diminished markedly in size. The patient remained asymptomatic for 14 months until January of 1960 at which time a painful perineal recurrence was again noted. She was treated with 5.0 gm. of 5-fluorouracil with no change in her lesion; a marked systemic reaction occurred. Because of increasing perineal pain and ulceration, she was retreated by further cobalt 60 beam therapy to the perineum to 4,500 r in 22 days in June, 1960. The immediate result was good in that the perineal pain and discharge ceased and the patient was able to return to teaching. Later on, the perineum became necrotic and sloughed, leaving a large cavity. Despite this, she was able to teach until March of 1961. She died in November of 1961, almost 3 years after her original treatment for perineal recurrence.

Comment. Both courses of therapy produced good palliation in that the patient was able to return to her work on each occasion for an appreciable period of time.

CASE 5. P.B., a 40 year old white male truck driver, had had a colostomy in March of 1958 and a Miles resection in August of the same year. In May of 1960 he presented with pain and several masses in the perineum, the largest of which measured 7×4 cm. The recurrence caused so much discomfort that he was forced to give up his work. He was treated with cobalt 60 irradiation receiving a dose of 5,000 r in 3½

TABLE I

CASE MATERIAL

Case	Age	Date of Original Procedure	Interval between Surgery and Perineal Recurrence	Nature of Recurrence	Treatment	Result	Duration of Palliation	Interval between Beginning of Radiation Therapy and Death	Grading of Result
1	57	Miles resection April, 1957	20 mo.	Pain and areas of induration in perineum	(a) 5,500 r in 29 days, 11×10 cm. portal (b) 5 gm. of 5-fluorouracil (c) 4,500 r in 20 days, 10×10 cm. portal	Good relief and disappearance of the mass for 14 mo. Recurrence in perineum and then retreatment with early pain relief and later necrosis	26 mo.	35 mo.	Good
2	67	Miles resection September, 1958	13 mo.	Induration and mass in the perineal scar	5,600 r in 28 days, direct perineal 8×8 cm. portal	Excellent with complete disappearance of the mass and total pain relief	12 mo.	12 mo.	Excellent
3	42	Cystectomy and Miles resection September, 1958	12 mo.	Pain and discharging mass with deep cavity in perineum	(a) 4,500 r in 35 days, opposed 14×12 cm. portals (b) 5.5 gm. of 5-fluorouracil	Shrinkage of cavity with good pain relief	22 mo.	22 mo.	Good
4	60	Miles resection April, 1959	8 mo.	Discharging mass in the perineum with severe pain in the thighs	4,500 r by 180° rotation, 13×7 cm. portal and 1,500 r via 15×9 cm. posterior portal	Complete relief of pain and slight lessening of discharge	8 mo.	8 mo.	Good
5	40	Colostomy March, 1958. Miles resection August, 1958	26 mo.	4 separate perineal masses, largest 7×4 cm.	5,000 r in 24 days, 15×10 cm. perineal portal	Diminution of nodules to ½ original size. Excellent pain relief	18 mo.	24 mo.	Good
6	59	Miles resection August, 1959	10 mo.	Perineal drainage	(a) 5 gm. of 5-fluorouracil (b) 4,500 r in 24 days, 10×10 cm. portal	Complete cessation in drainage. Significant palliation	5 mo.	5 mo.	Fair
7	68	Miles resection February, 1960	3 mo.	Severe pain in leg with mass in buttock and in perineum	(a) 2,150 r in 11 treatments (b) 3.5 gm. of 5-fluorouracil	Marked radiation reaction with moist desquamation forcing stoppage of treatment. Relief of pain for 12 mo. than recurrence in vagina with bleeding	12 mo.	21 mo., still alive	Good
8	60	Miles resection March, 1961	10 mo.	4 cm. mass in the perineum with severe pain in the area	5,400 r in 28 days, 10×10 cm. perineal portal	Excellent pain relief. No real objective changes in the mass	18 mo.	21 mo., still alive	Good
9	72	Pullthrough procedure December, 1959, followed by radiation therapy to pelvis	24 mo.	Edema and tenderness in perineum. Patient was uremic with liver metastasis	2,400 r in 7 days, 8×6 cm. perineal portal	Slight regression of perineal mass	0	2 wk.	Poor
10	67	Colostomy July, 1958, Cordotomy October, 1961	42 mo.	Severe pain in gluteus muscle with mass and induration	3,600 r 17×15 cm. perineal portal and 2,400 r 15×10 cm. opposed lateral portals	Marked tumor regression with good pain relief	5 mo.	5 mo.	Fair
11	72	Miles resection January, 1962	5 mo.	Ulceration of multiple perineal masses	2,900 r in 13 days, 13×12 cm. perineal portal	Patient uremic, BUN 220. No real response	0	3 wk.	Poor
12	66	Miles resection May, 1961	14 mo.	Pain in the perineum with multiple nodules in perineum and vagina	3,500 r in 29 days, 17×12 cm. perineal portal	No objective or subjective changes noted	0	2 mo.	Poor
13	54	Miles resection June, 1960	26 mo.	Enlarging painful mass in perineum	5,000 r in 28 days, 8×8 cm. perineal portal	Slight regression at first, then immediate recurrence with severe pain. Infused with 5-fluorouracil	2 mo.	7 mo., still alive	Poor

Table II

EVALUATION OF RESULTS IN PERINEAL RECURRENCE

Excellent	Complete relief of pain and regression of lesion for 6 months
Good	Marked relief of symptoms and regression of lesion for at least 6 months with later recurrence in perineum
Fair	Pain relief for 3 months but no objective regression
Poor	Failure or death within 3 months

weeks through a 15×10 cm. direct perineal portal. Complete pain relief was achieved. The masses shrank to about half their original size and the patient returned to work. Improvement was maintained for 18 months until generalized metastases occurred. He was given a course of 5-fluorouracil with no improvement and died in June of 1962, approximately 2 years after the beginning of therapy.

Comment. We consider this a good result, with 18 months of relatively comfortable existence during which time he was able to do his work.

Case 9. C.R., a 72 year old white male, had had a pullthrough procedure for rectal carcinoma in December of 1959. He received 250 kv. irradiation for a pelvic mass in 1960. He presented to our department in December of 1961 with a soft tissue mass in the perineum. He was uremic and an I^{131} rose bengal liver scan was positive for liver metastasis. He was treated with cobalt 60 beam radiation to 2,400 r in 7 days by means of an 8×6 cm. portal. Pain relief was minimal and the patient died 2 weeks after the end of therapy.

Comment. This represents one of our poor results and emphasizes the importance of a patient's general condition in deciding upon a specific palliative measure.

Case 10. M.H., a 67 year old white male, had a colostomy for carcinoma of the rectosigmoid area in July of 1958. Perineal recurrence caused severe anal pain and cordotomy was necessary in October of 1961. This failed to relieve his symptoms and he presented to our department in December of 1961. At that time, he had a 6 cm. mass in the gluteus muscle area and marked tenderness. He received 3,600 r by means of a direct 17×15 cm. portal and 2,400 r through opposed 15×10 cm. lateral portals. There was some tumor regression and good pain relief until he died in June of 1962 from generalized metastases.

Comment. We consider this a fair result with effective short term palliation.

Case 13. J.P., a 54 year old white male, had a Miles resection in June of 1960 and perineal recurrence in September of 1962. When he was seen in the department, he had an enlarging painful mass in the perineum but no other evidence of recurrent disease. He seemed a good candidate for treatment and was given 5,000 r in 28 days through an 8×8 cm. direct perineal portal. There was good regression and pain relief at first, but almost immediately, both the pain and the mass recurred, necessitating neurosurgical intervention. This also failed and an infusion with 5-fluorouracil into the hypogastric artery was done with good early results.

Comment. We consider this a treatment failure and the only patient in our series who had a full course of radiation therapy without significant palliation.

RESULTS

In our series, we feel that 9 out of 13 patients received worthwhile palliation from the cobalt 60 treatments. It is interesting to note that in 3 of our treatment failures, the patients' condition was near terminal thus causing us to curtail our dose. Of all the cases in which we were able to take the patients to the full prescribed dose, only 1 (Case 13) failed to show a satisfactory result. The use of 5-fluorouracil in conjunction with the irradiation did not alter the results.

We noted no problems in managing skin reactions in the majority of our patients. In only 1 (Case 7) was the reaction severe

Table III

RESULTS

Excellent	1
Good	6
Fair	2
Poor	4
	13

enough to cause us to discontinue treatment. In all of the other patients the reaction was easily managed by the usual principles of local care.

DISCUSSION

Several authors have recently written on the spread and sites of rectal carcinoma recurrences. These papers emphasize the importance of local recurrence in the late symptomatology and management of this disease. Taylor[12] and Gilbertsen[3] have reviewed the problems of local recurrence in detail. Gilbertsen followed 125 cases to death and found a recurrence rate of 74 per cent with 51 per cent of these representing local disease. In his series, the most common site of recurrence in women was in the cul-de-sac, while males tended to have recurrences in the posterior pelvis, and precoccygeal and sacral plexus. Gilbertsen's series included 5 perineal recurrences. Seefeld and Bargen[10] analyzed 100 operative specimens and found the highest local recurrence rate associated with invasion of the perineural space by tumor cells. The patients with perineural invasion also had the worst prognosis. Dukes and Bussey[1] stressed the poor prognosis associated with lymph node invasion.

These studies emphasized the importance of the local spread and recurrence. Nevertheless, the radiologic literature is rather sparse on the treatment of these problems. Henschke's work has already been alluded to. He treats perineal recurrence with interstitial applications of radioactive materials in order to minimize the skin reactions. Williams *et al.*[15] using a 1,000 kv. beam treated 28 cases of perineal recurrence and felt that significant palliation was achieved in most cases. He noted an average symptomatic improvement of 7.7 months. Wise and Smedal[16] used a 2 mev. Van de Graaff generator and achieved good results. They concluded that the primary treatment was worthwhile, but retreatment rarely so. Their dose ranges were essentially similar to those which we used. Jaffe and Gazzaniga[6] and Wang and Schultz[13] used smaller doses (3,000 r) for problems such as rectal discharge, bleeding and recurrent mass at a bowel anastomosis.

In our own series, the best results were achieved in patients whose recurrence was limited to the perineum. Their survival times (average 13 months) are long enough to make palliation in the form of pain relief and return to a relatively normal life a worthwhile aim.

SUMMARY

Thirteen cases of perineal recurrence of carcinoma of the rectum and colon treated palliatively by cobalt 60 irradiation are reported. Nine patients had worthwhile palliation. Radiation therapy should probably not be given where severe generalized disease coexists with perineal recurrence.

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PERIPHERAL BONE METASTASES*

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PERIPHERAL bone metastases are rare lesions; when these occur they are often from a primary carcinoma of the lung.[3-7,9,12] Considering the frequent involvement of bone by metastatic disease, the rarity of these peripheral lesions is quite unique. Jaffe, in his discussion of osseous metastases, has stated, " . . . it is only exceptionally located in a bone distal to the knee joint and hardly ever in a bone distal to the elbow joint."[8] In spite of their rarity, these metastatic processes should be included in the differential diagnosis of lytic lesions of the bones of the hands and feet. Six cases of peripheral metastases are reported and the roentgenographic features and probable mechanism of production are discussed.

REPORT OF CASES

CASE I. A 60 year old white male with a biopsy proven squamous cell carcinoma of the lung complained of pain and swelling in the tip of his fifth finger. Clinically, this was thought to represent an inflammatory process.

A roentgenogram of the digit revealed expansion and extensive destruction of the terminal phalanx by a homogeneous soft tissue mass which had replaced almost the entire bone. A few fragments of cortical bone were noted at the periphery of the soft tissue mass and a thin rim of subchondral bone was still present at the joint (Fig. 1).

Histologically, tissue from the phalangeal lesion appeared identical with that of the primary pulmonary carcinoma.

CASE II. A 68 year old white female presented with pain in the left neck and shoulder. Physical examination and plain roentgenograms of these areas were unremarkable. Because of aggravation of her symptoms and the appearance of neurologic changes, a myelogram was made one month later. This showed an extradural defect on the left displacing the spinal cord and destruction of the adjacent vertebral pedicle (Fig. 2*A*). A chest roentgenogram revealed an ill-defined pulmonary nodule suggestive of a primary malignancy.

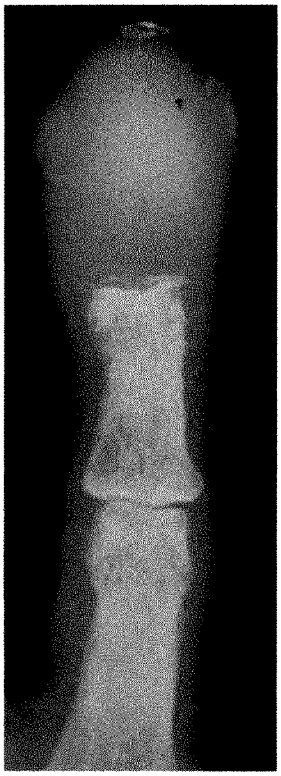

FIG. 1. Case I. Roentgenogram showing metastasis to the distal fifth phalanx.

Twenty-two months after the onset of symptoms, the patient complained of painful swelling of the proximal portion of her index finger. A roentgenogram (Fig. 2*B*) revealed extensive bone destruction and expansion of the phalanx by a large, well defined soft tissue mass. There was relatively normal bone in the distal portion of the phalanx and a thin line of cortical bone remained at the proximal joint.

Surgical specimens from the spine, lung and finger were all reported by the pathologist as adenocarcinoma. The pulmonary lesion was thought to be the primary one and no evidence of a primary site elsewhere was demonstrated.

CASE III. A 61 year old white male, ap-

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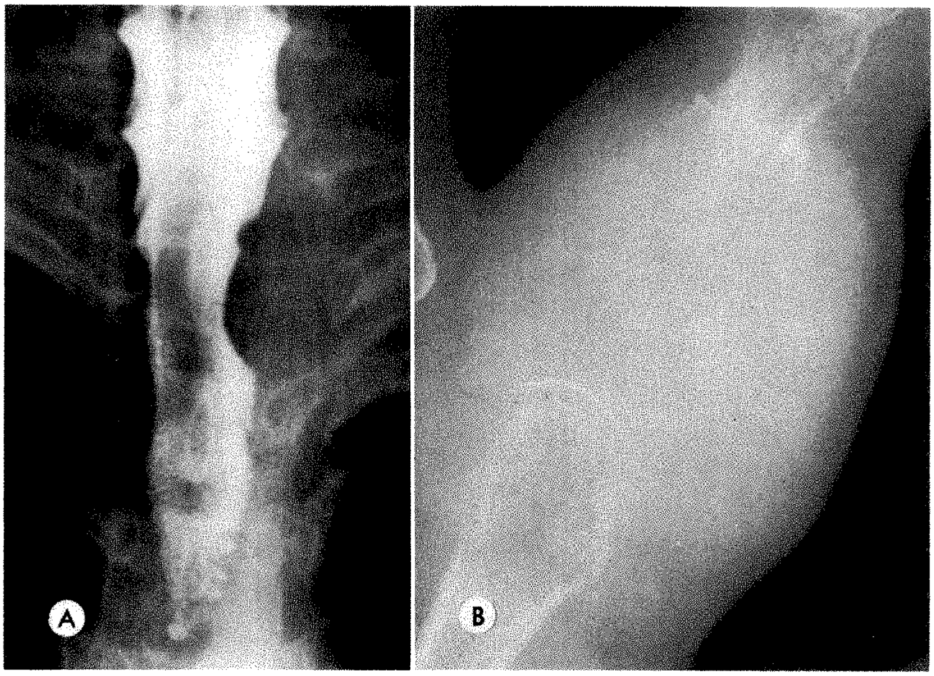

Fig. 2. Case II. (*A*) Roentgenogram showing the extradural defect with destruction of the vertebral pedicle and displacement of the spinal cord. (*B*) Roentgenogram showing metastatic destruction of the proximal phalanx of the index finger.

parently in good health, was admitted for evaluation of hoarseness and a cough productive of mucoid material. While in the hospital, he noted pain in his left foot. There was redness, swelling, heat and tenderness in the region of the cuboid.

A chest roentgenogram revealed enlargement and increased density of the left hilus and partial atelectasis of the left upper lobe. A roentgenogram of the left foot (Fig. 3) showed extensive destruction of the medullary bone of the cuboid with a thin rim of remaining cortex and relatively normal structure of the remaining trabeculae.

At operation a dense mass of gelatinous material was found replacing the normal internal structure of the bone; a thin shell of remaining cartilage surrounded this tissue. A biopsy was reported as metastatic squamous cell carcinoma, probably of pulmonary origin.

On this same admission, a polyp of the urinary bladder was removed and its base fulgurated. Microscopically, there was an area of purely transitional cell carcinoma on the apex of the polyp, but there was no involvement of its stalk. There was no epidermoid transition in this lesion and the pathologist thought that this was unrelated to the metastatic lesion of the cuboid.

Case IV. A 62 year old white male was admitted because of progressive, painful swelling of 3 months' duration, in his right foot. He had had a chronic productive cough and had lost 21 pounds in the 3 month period.

There was redness, swelling, heat and marked tenderness in the region of the first cuneiform. Physical examination was otherwise noncontributory.

A roentgenogram of the right foot (Fig. 4) revealed almost complete destruction of the first cuneiform. The admission chest roentgenogram demonstrated a mass extending from the left hilus into the left upper lung field and there was partial atelectasis of the left upper lobe; the roentgenographic changes were interpreted as "probable bronchogenic carcinoma."

A needle biopsy of the lytic lesion of the first cuneiform was reported as epidermoid carcinoma, probably of bronchial origin.

There was progressive debility and cachexia and the patient expired 7 months after the onset of symptoms.

Autopsy revealed a large neoplasm occupying most of the left upper lobe. The rupture of a necrotic cavity within the tumor into the pleural space was thought to be the terminal event. There was partial obstruction of the left upper lobe bronchus by a friable, fungating, intraluminal component of the malignant mass. Microscopically, this was a primary epidermoid carcinoma; it was histologically indistinguishable from the biopsy of the left foot. There were focal metastases in the left adrenal gland and in the cortex of the left kidney.

Case v. A 69 year old white male was seen because of progressive cough and weakness. A chest roentgenogram revealed a mass lesion of the right lower lobe. An inoperable squamous cell carcinoma with extensive pleural involvement was found on exploration and the chest was closed. Some symptomatic improvement occurred following antimetabolite therapy.

Four months after the initial admission, the patient complained of progressive, painful swelling of his left fourth finger. The proximal portion of this digit was swollen and tender, and the skin was tense and erythematous. Clinically, this was thought to represent an inflammatory process.

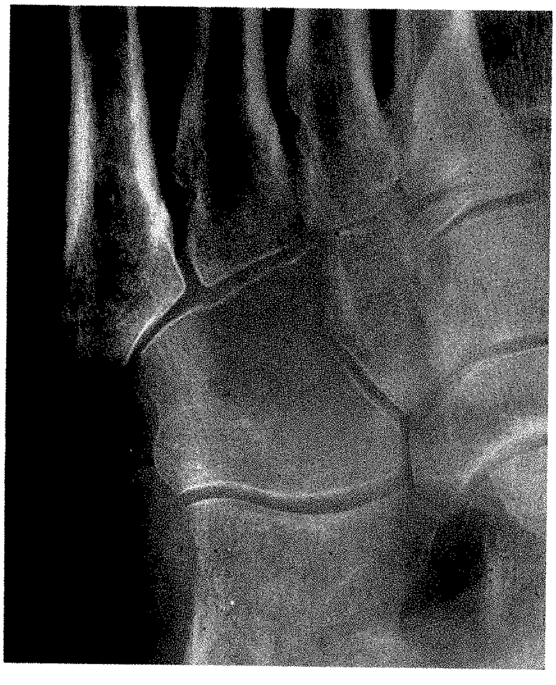

Fig. 3. Case iii. Roentgenogram showing medullary destruction of the cuboid by a bronchogenic metastasis.

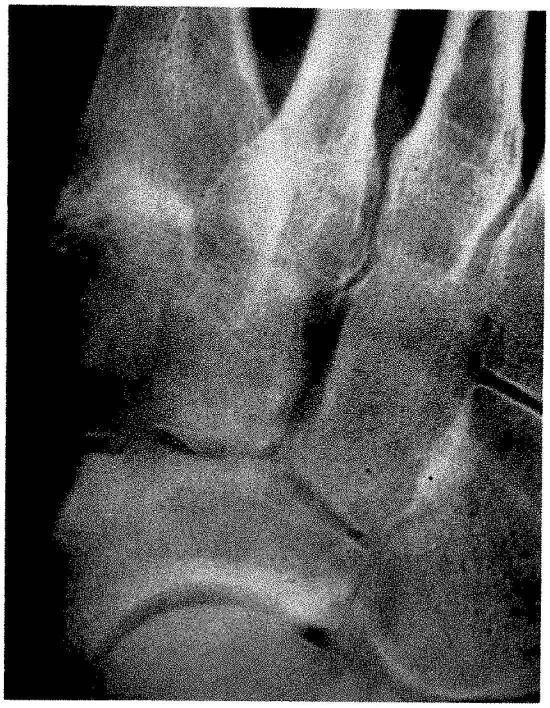

Fig. 4. Case iv. Roentgenogram showing destruction of the first cuneiform by metastatic carcinoma.

A roentgenogram of the hand (Fig. 5) demonstrated medullary destruction of the proximal fourth phalanx with complete loss of the bony cortex and an adjacent homogeneous soft tissue mass. Some less definite changes of the medullary bone of the phalanges of the fifth finger were present. Regression of the pain and swelling occurred following radiation therapy to the finger, but the patient's condition deteriorated and he expired after a febrile downhill course.

Autopsy revealed a large abscess distal to an obstructing carcinoma of the right lower lobe bronchus. There was malignant extension to the pericardium and bilateral adrenal metastases were found.

Case vi. A 32 year old white female presented with relatively sudden loss of visual acuity in her right eye. A retinal detachment was thought to be due to a metastatic malignancy by the ophthalmologist. A routine chest roentgenogram revealed increased size and density of the lower part of the left hilus and a laminagram of that area demonstrated narrowing of the left lower lobe bronchus and an associated soft tissue mass.

Biopsies of the endobronchial lesion and

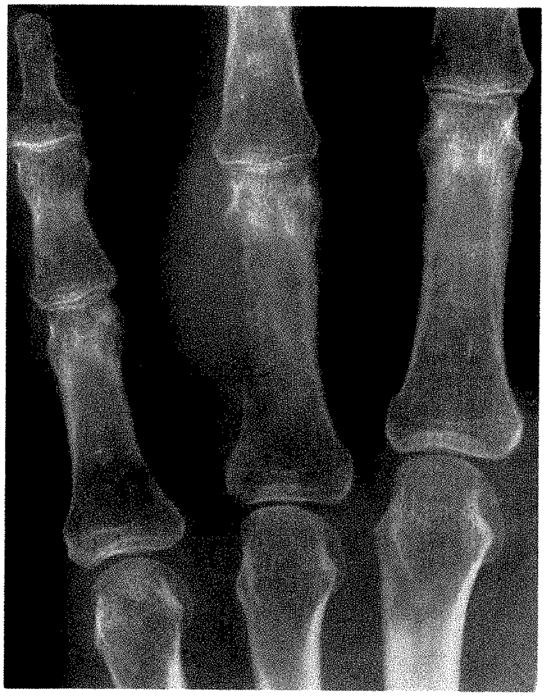

FIG. 5. Case v. Roentgenogram showing bronchogenic metastasis to the proximal fourth phalanx.

subcutaneous nodules were reported as undifferentiated carcinoma.

While receiving radiation therapy to her eye and lung lesions, the patient noted pain in the tip of her left middle finger. A roentgenogram (Fig. 6*A*) revealed destruction of the medullary bone of the terminal phalanx. Radiation therapy resulted in remission of pain and reossification of the area of destruction (Fig. 6*B*). Pathologic proof of the peripheral bone lesion was not obtained in this case. Debility was ingravescent and the patient expired from bronchial hemorrhage 4 months after the onset of symptoms.

At autopsy multiple metastases were found in both lungs, the myocardium, uterus, spine, spleen, liver, and both kidneys. A large left hilar mass was thought to represent the primary site. The pulmonary veins were dissected from the left atrium to the lungs; a large, friable, intraluminal component of the malignant mass was found occluding the pulmonary vein which drained the left lower lobe. Clumps of intra-arterial tumor emboli were identified microscopically in sections from various tissues.

Malignant tumor emboli, carried by the pulmonary vein to the left atrium and entering the systemic arterial circulation, would explain the widespread metastases in this patient.

DISCUSSION

Metastases in the bones of the hands and feet are rare, but may occur. The bones of the foot are involved more often than those of the hand, and cases of multiple lesions have been reported. These lesions usually occur in the phalanges, especially the terminal ones, and have been previously reported in the tarsal bones; no record of a

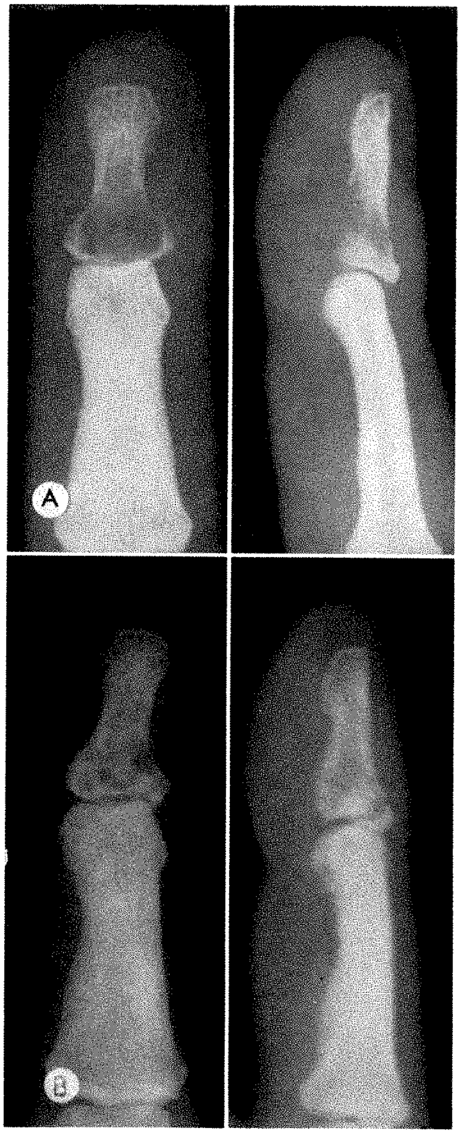

FIG. 6. Case VI. (*A*) Roentgenogram showing an osteolytic lesion of the terminal phalanx of the middle finger; primary bronchogenic carcinoma. (*B*) Roentgenogram showing reossification of the area of destruction following radiation therapy.

carpal bone metastasis could be found.[9] It is thought that these metastases are always symptomatic and, as in Case IV, may be the first evidence of a malignant process.

In all of the present cases and in most of those previously reported, these metastases have closely simulated osteomyelitis both clinically and roentgenologically. The roentgen characteristics of these lesions, while not pathognomonic, are fairly typical and should suggest the correct diagnosis. Peripheral bone metastases are purely osteolytic and the reactive condensation of bone which may occur in osteomyelitis has not been observed. Periosteal reaction, commonly seen in inflammatory processes, does not occur with these metastatic lesions. The trabecular destruction produced by the metastasis is usually well defined and the surrounding trabeculae are relatively normal in appearance. In osteomyelitis there is usually demineralization and smudging of fine trabecular detail in the reaction areas adjacent to zones of complete bone destruction. Peripheral metastases do not involve or cross the joint[4] and even with extensive destruction a thin margin of subchondral cortical bone usually remains. If the expanding mass of intramedullary neoplasm has broken through the thinned-out shell of remaining cortical bone, the adjacent soft tissue involvement is usually homogeneous, localized and well defined. In inflammatory processes, diffuse swelling, reticulation and obliteration of the subcutaneous fat line are the characteristic soft tissue changes. The ballooned-out effect on the remaining cortical shell produced by the expanding neoplastic mass is not seen in osteomyelitis.

In all 6 of the reported cases and in about half of those found in the literature, the primary malignancy has been in the lung.[12]

The striking rarity of metastases in the peripheral bones, in spite of the frequency of osseous involvement in carcinomatosis, may be related to the usual mechanism of hematogenous spread. Primary malignancies commonly erode veins and venous transport of malignant emboli to the capillary filter beds of the lungs or liver can occur.[11] The communications of the vertebral venous plexus permit, in addition, the deposition of these tumor emboli in the axial skeletal structures.[1,2] The more peripheral bones, however, do not share in this sluggish, reversible system of venous anastomoses, and even with extensive metastatic involvement of the axial skeleton the peripheral bones are rarely affected. Venous erosion by a pulmonary malignancy, however, may result in the hematogenous transport of tumor emboli to the left heart and from there to the systemic arterial distribution.[11] The arterial dissemination of malignant foci in this manner could account for the rapid appearance of metastases in usual areas (including the peripheral osseous structures) not infrequently seen with primary pulmonary malignancies.

This mechanism of peripheral metastasis has been pointed out in the past[5] and the autopsy findings in Case VI are evidence for this type of dissemination. Similar cases with metastases in unusual areas, in addition to the phalanges, have been reported.[3] Experimentally, such widespread metastases have been produced in rabbits by the injection of tumor cells into the left ventricle. In these animals the number of metastases produced in a given organ were proportional to the blood flow to that organ.[10] The relatively profuse arterial flow in the distal portions of the digits may explain the predilection of these metastases to occur in the terminal phalanges.

SUMMARY

Peripheral bone metastases are rare, but can occur and should be included in the differential diagnosis of osteolytic lesions of the hands and feet. Six cases, all associated with primary pulmonary malignant neoplasms are reported.

These lesions may closely simulate osteomyelitis; some differential roentgen features are described.

The probable mechanism of production of these lesions is discussed and autopsy support of this mechanism in one of the cases is presented. The tendency of these metastases to occur in the terminal phalanges may be related to the brisk arterial flow to the ends of the digits.

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The author wishes to thank Dr. Benjamin Felson for his helpful comments and Dr. Warner Peck for the use of Case III.

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OSTEOBLASTIC METASTASES FROM BRONCHOGENIC CARCINOMA*

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BONE metastases are not uncommon with bronchogenic carcinomas. The incidence of bone invasion varies from 25 to 32 per cent in some series.[3] In one series of 1,000 consecutive autopsied cases of bronchogenic carcinoma, there were 27.2 per cent with skeletal metastases.[1] These metastatic lesions are classically osteoclastic. Some authors do not even consider bronchogenic origin for osteoblastic metastatic lesions.[3] There have been numerous reports of bizarre syndromes associated with bronchogenic neoplasms; these include hypocalcemia and hypercalcemia, and a variety of endocrine disturbances.[2,4,5]

We wish to call attention to a recognized, but little appreciated, aspect of metastatic bronchogenic carcinoma; namely, osteoblastic bone lesions, of which several single cases have been reported.[3,4,5] We have collected 5 cases of histologically proven osteoblastic metastases from bronchogenic carcinoma.

REPORT OF CASES

CASE I. A 37 year old white male entered the hospital with a history of severe dyspnea on exertion and bilateral sharp chest pains, not related to exercise, of 3 months' duration; there was also a 60 pound weight loss and marked anorexia during this time.

Physical examination revealed a chronically ill, thin, white male. Vital signs were normal except for a temperature of 100.5°F. Significant abnormalities were: tracheal deviation to the left, decreased breath sounds over the left anterior chest field, and a large, irregular liver extending 5 cm. below the right costal margin. Small lymph nodes were palpated in the anterior cervical region. The hemoglobin was 10.3 gm. per cent, and the white blood cell count 35,000 with an increase in neutrophils. The serum alkaline phosphatase was 18.3 King-Armstrong units.

A chest roentgenogram (Fig. 1) showed a large mass obscuring the left hilus and extending peripherally to involve the mid-third of the lung. A small pleural effusion was also present. The posterior portion of the right fifth rib was uniformly sclerotic, and the anterior portion showed evidence of destruction. Osteolytic and osteoblastic metastases were seen on roentgenograms of the spine and pelvis. The patient was given radiation therapy to the areas of bone pain. He continued to deteriorate and expired 5 months following admission.

Postmortem examination revealed a primary bronchogenic carcinoma of the left upper lobe with widespread visceral and skeletal metastases. The neoplasm was composed of sheets of small and closely grouped cells with scanty cytoplasm and round or oval hyperchromatic nuclei. The bone metastases showed replacement of the marrow spaces by clusters of anaplastic cells supported by delicate fibrous septa. Evidence of new bone formation was present (Fig. 2).

CASE II. A 44 year old white male entered the hospital because of neck swelling, dyspnea, weakness, and anorexia of 9 months' duration. Physical examination showed evidence of marked weight loss. There was decreased tactile fremitus and absent breath sounds over the right posterior base. The liver was nodular, tender, and enlarged 4 cm. below the right costal margin. The laboratory findings were noncontributory except for an alkaline phosphatase of 27 King-Armstrong units.

Chest roentgenograms revealed an irregular mass at the right base and suggestive enlargement of the right hilar shadow. A roentgenogram of the dorsal spine showed dense sclerosis of the spinous process of T3 and increased density of the left side of the body of T4, including the pedicle (Fig. 3). He expired 2 months after admission.

Postmortem examination revealed an anaplastic carcinoma of the right lower lobe with metastases to the liver, adrenals, lymph nodes and vertebrae. The bone metastases showed nests of closely grouped neoplastic cells in a

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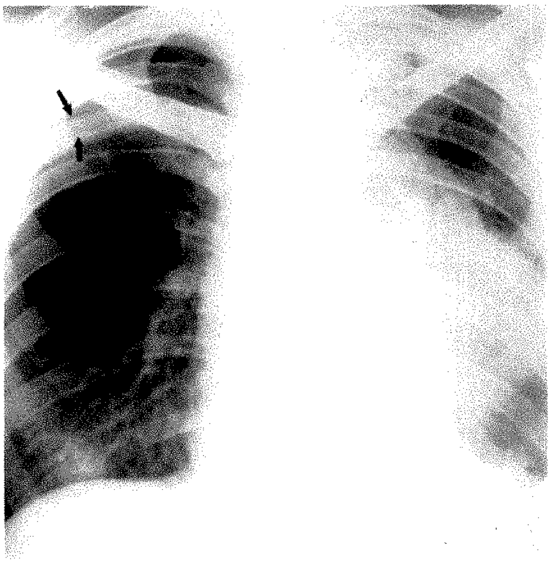

FIG. 1. Case I. Primary bronchogenic carcinoma on left. Osteoblastic metastasis to right posterior fifth rib (arrows).

loose fibrous stroma. There was evidence of new bone formation about the tumor cells.

CASE III. A 53 year old white male was admitted to the hospital with an 8 week history of anorexia, weight loss, and severe upper abdominal pain not related to food intake. Physical examination revealed a thin male appearing chronically ill. The vital signs were normal. There was a constant expiratory wheeze heard over the right lower lung field posteriorly. The liver was enlarged and tender. The laboratory studies were normal, except for an alkaline phosphatase of 16.4 King-Armstrong units.

Chest roentgenograms revealed a mass in the superior segment of the right lower lobe with enlargement of the homolateral hilus. Examination of the spine disclosed diffuse, nonhomogeneous increase in density of the body of T12 (Fig. 4).

The patient was given several courses of nitrogen mustard, but his condition deteriorated rapidly, and he expired 8 months after admission.

Postmortem examination revealed a primary bronchogenic carcinoma of the right lower lobe with widespread visceral and skeletal metastases. The neoplasm presented a variable histologic picture with areas of definite adenocarcinoma. The histology of the metastases, including that of the bones (Fig. 5), was similar to that of the primary lesion.

CASE IV. This 48 year old white male entered the hospital because of sticking pain in the chest of 3 weeks' duration; there was also marked dyspnea, fatigability, and anorexia of several months' duration. Physical examination revealed a well nourished male in no acute dis-

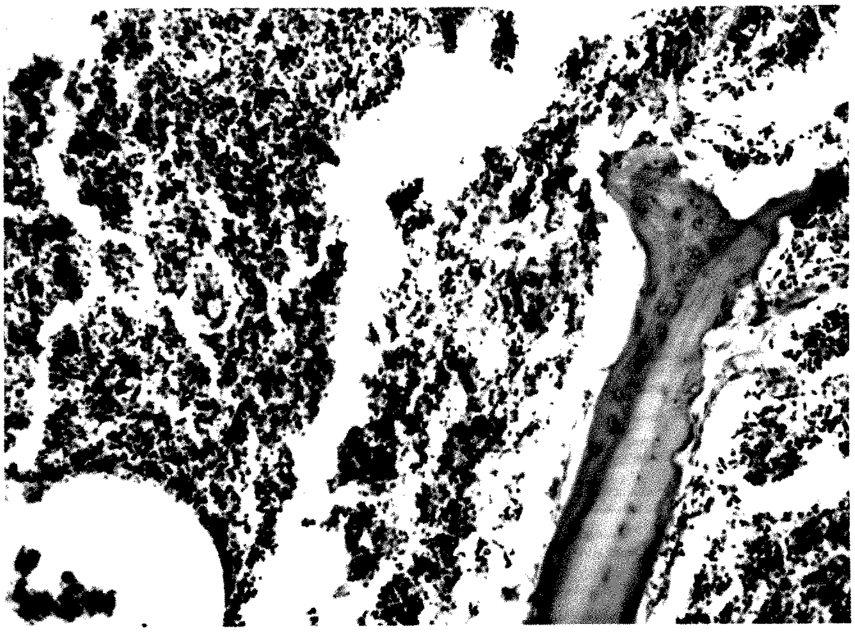

FIG. 2. Case I. Photomicrograph of bone metastasis showing sheets of tumor cells. The bone trabecula is thickened by apposition of new bone (×120).

tress. The breath sounds were decreased over the upper two-thirds of the right lung. Rectal examination revealed a normal sized prostate. The laboratory findings were normal except for the alkaline phosphatase level which was 24.4 King-Armstrong units. The acid phosphatase level was normal.

Roentgenograms of the chest showed a right parahilar mass with confluent patchy infiltration in the right upper lobe. A right paratracheal soft tissue mass suggested lymph node metastases. The diaphragm was elevated on the same side. Extensive osteolytic and osteoblastic metastases were seen in the spine, pelvis, ribs and shoulder girdles (Fig. 6, *A* and *B*).

An exploratory thoracotomy disclosed an infiltrating mass in the superior segment of the right lower lobe with invasion of the adjacent chest wall and mediastinal structures. Biopsies of the lung and pleura were taken during this procedure and showed adenocarcinoma (Fig. 7). At a later date a bone biopsy from the iliac crest revealed fibrosis of the marrow spaces. The fibrous tissue was diffusely infiltrated with neoplastic glands (Fig. 8). Needle biopsy of the prostate gland showed normal histology. This patient expired, but permission for autopsy was not granted.

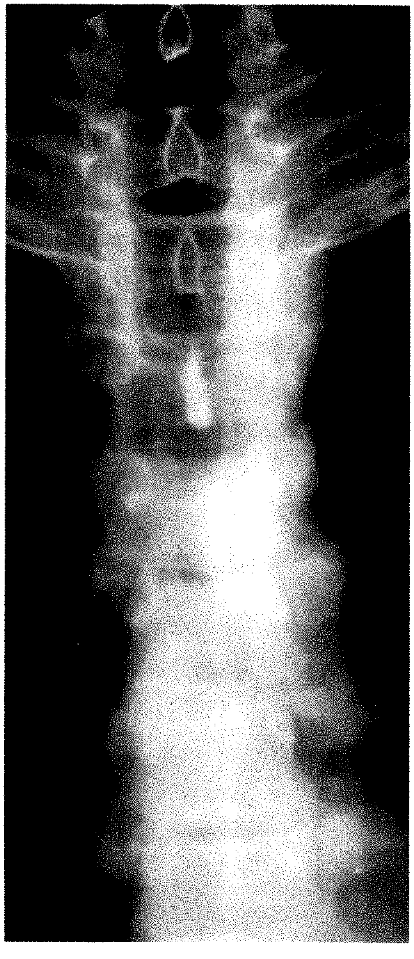

FIG. 3. Case II. Osteoblastic metastases to spinous process of T3 and body of T4.

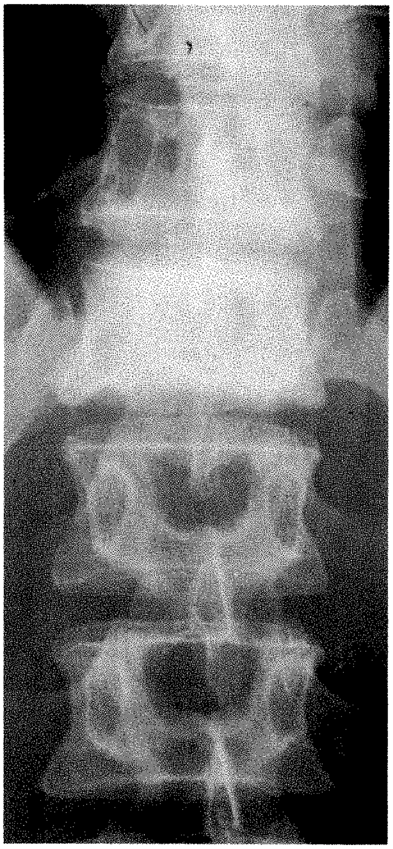

FIG. 4. Case III. Osteoblastic metastasis to body of T12.

CASE V. This 61 year old white male was admitted to the hospital because of severe dyspnea of several months' duration. Physical examination revealed markedly emphysematous lungs with inspiratory and expiratory wheezing bilaterally. There were no breath sounds over the lower left lung field posteriorly. The fingers showed moderate clubbing and marked cyanosis of the nail beds. The remainder of the examination and the laboratory findings were noncontributory except for an alkaline phosphatase of 36 King-Armstrong units, and a serum acid phosphatase level of 4.1 Guttman units. The chest roentgenograms showed a homogeneous opacity obscuring the lower half of the left lung field, which consisted of a mass

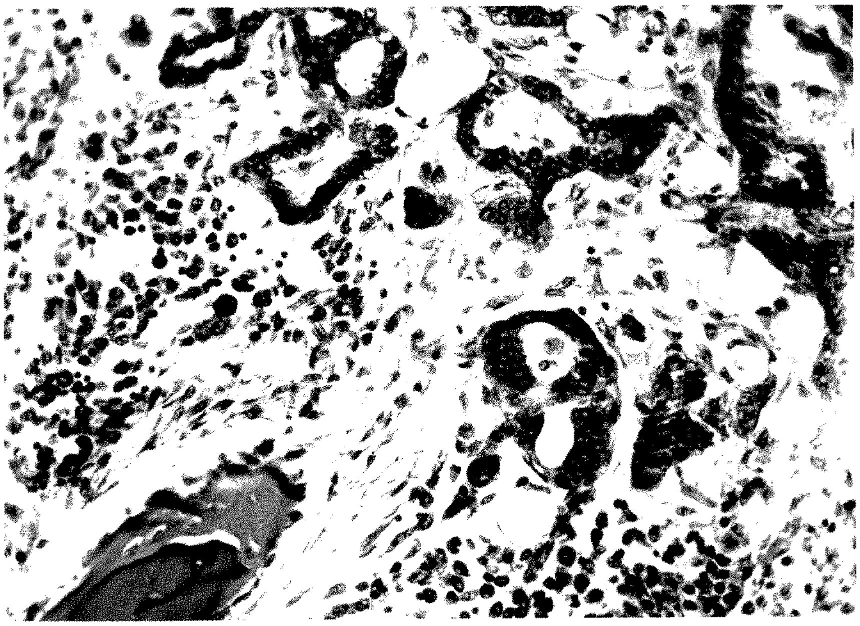

FIG. 5. Case III. Photomicrograph of bone showing metastatic adenocarcinoma. At the left lower angle is a bone trabecula capped with newly formed osteoid (×225).

in the lower lobe plus a pleural effusion. A bone survey revealed multiple discrete and coalescent nodular osteoblastic lesions in the spine, pelvis, and several of the long bones (Fig. 9, *A* and *B*). The patient expired 11 months after admission.

Postmortem examination revealed a primary bronchogenic carcinoma of the left lower lobe with metastases to the liver, spleen, adrenals, and lymph nodes. The primary lesion in the

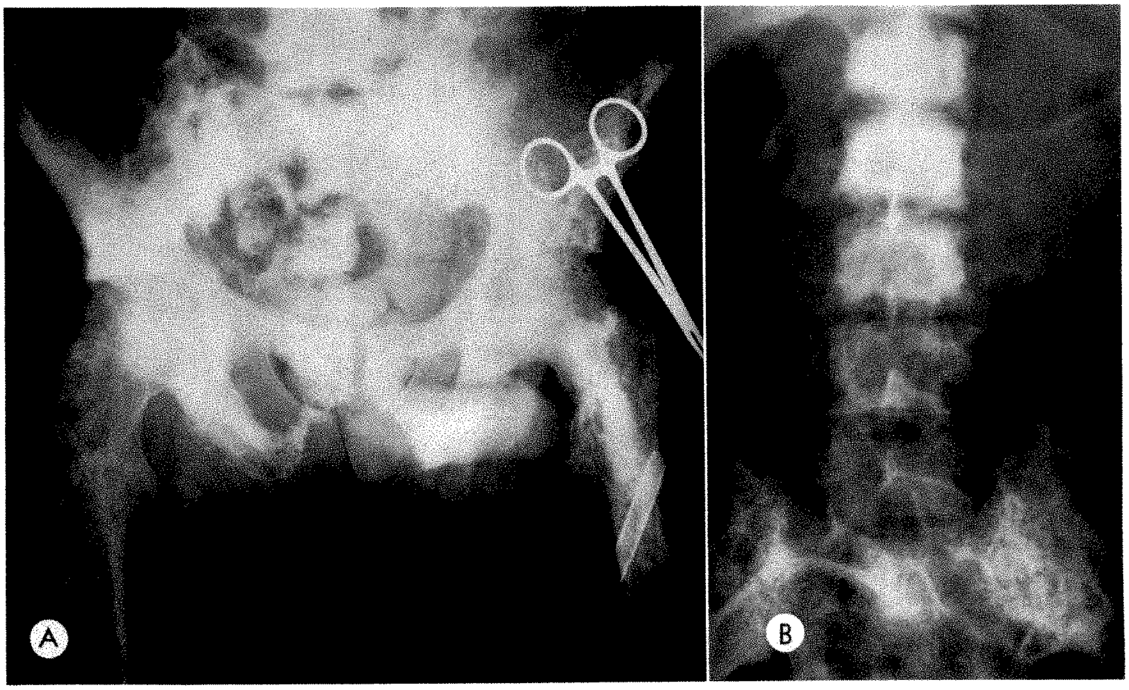

FIG. 6. Case IV. (*A*) Combined osteoblastic and osteolytic metastases to lumbar spine, pelvis and femurs. (*B*) Combined osteoblastic and osteolytic metastases to lumbar spine and pelvis.

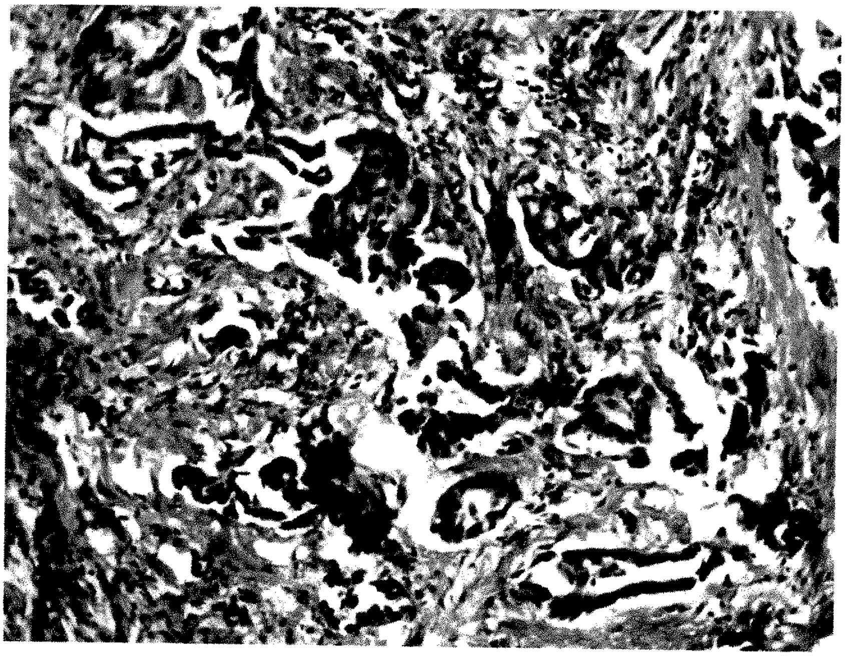

Fig. 7. Case iv. Photomicrograph of pleural biopsy showing marked fibrous thickening and infiltration by variously shaped neoplastic glands (×120).

lung was composed of epithelial cells arranged in variously shaped glandular structures. The bone metastases showed areas of marrow replacement by fibrous tissue containing neoplastic glands.

DISCUSSION AND CONCLUSION

The primary purpose of this communication is to report 5 cases of osteoblastic metastases from primary bronchogenic car-

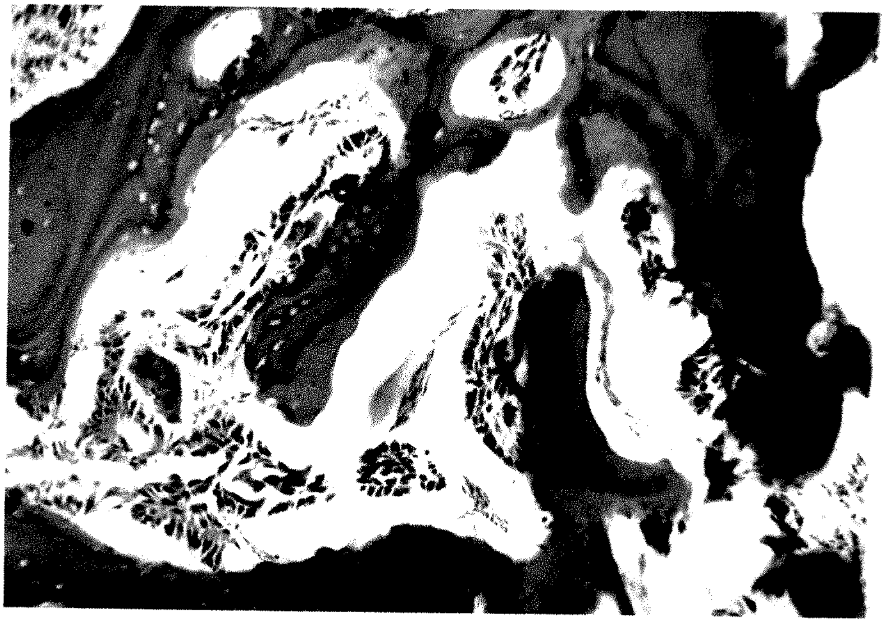

Fig. 8. Case iv. Photomicrograph of iliac bone biopsy showing elongated neoplastic glands in the marrow spaces. Note the apposition of newly formed bone causing widening of the trabeculae (×120).

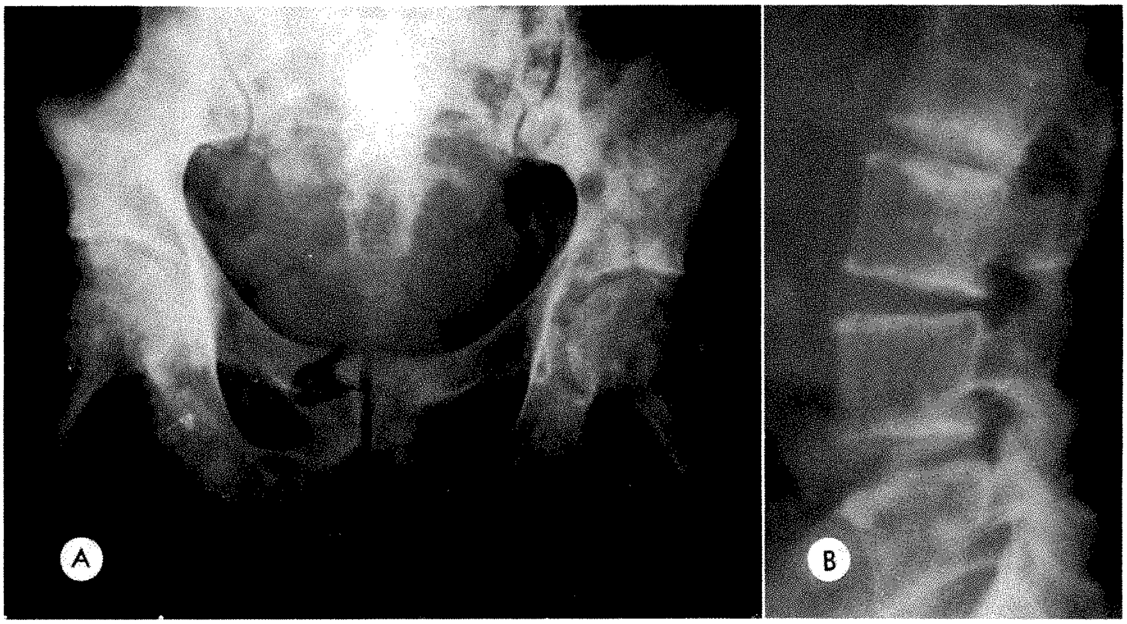

Fig. 9. Case v. (*A*) Nodular osteoblastic metastases to pelvis. (*B*) Nodular osteoblastic metastases to lumbar spine.

cinoma. Of these, 2 were anaplastic and 3 were adenocarcinoma. Although adenocarcinoma of the lung constitutes only about 13 per cent of all primary bronchogenic carcinomas,[6] this type has been most frequently associated with osteoblastic metastases.

The roentgenologic appearance of the bone lesions in Cases iv and v is worthy of note. These lesions are indistinguishable from those due to metastases from prostatic cancer. In Case v, malignancy of the prostate was excluded post mortem by gross and microscopic examination. Postmortem examination was not performed in Case iv, but a primary carcinoma of the prostate, though not completely excluded, was considered unlikely based on the following findings: (a) normal size, shape and consistency on repeated rectal examination; (b) normal histology of the prostatic biopsy; (c) normal levels of serum acid phosphatase on two occasions; and (d) similarity of the lesions encountered in the pleuropulmonary and in the bone biopsies. In addition, the gross appearance of the lung tumor at exploratory thoracotomy was that of a primary rather than of a metastatic lesion.

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INTRACRANIAL EPENDYMOMAS[*]

A STUDY OF SURVIVAL IN 65 CASES TREATED BY SURGERY AND IRRADIATION

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EPENDYMAL tumors are usually classified with the glial neoplasms of the nervous system. They arise in those sites where ependymal cells normally occur; the lining of the ventricular system, the central canal of the spinal cord and the ventriculus terminalis in the conus medullaris. In addition, many clusters of ependymal cells are found in the filum terminale and at or near points of fusion of the angles of the ventricles. The purpose of this paper is to analyze the case histories of a large number of patients with primary intracranial ependymomas in order to evaluate the effect of surgery and radiation therapy upon the course of this disease. Spinal cord ependymomas seen at the New York Neurological Institute have been previously evaluated and are not included in this report.[25]

REVIEW OF LITERATURE

Among large series of intracranial gliomas, the incidence of ependymomas has varied from approximately 2 per cent[2] to 9 per cent.[22] The average age of 126 patients with intracranial ependymomas in the study of Mabon *et al.*[11] was 23.4 years; thus emphasizing their predominance in early life. Indeed, the supratentorial ependymoma is considered by some to be the most common cerebral hemispheral glioma of children.[18,26]

Ependymomas usually grow slowly and, as with other relatively benign neoplasms, the prognosis is in a large part dependent upon the location of the tumor. In various series approximately 60 per cent of intracranial ependymomas have been infratentorial in location.[2,8,18] Most of the tumors arise in the midline in the fourth ventricle. They often fill the fourth ventricle and frequently project extraventricularly into the cisterna magna. Extension about the upper segments of the cervical cord is relatively common, while spread into the cerebellopontine angle, into the central canal of the spinal cord and into and through the aqueduct of Sylvius occurs less frequently. The growth of supratentorial tumors is often by expansion toward the centrum semiovale rather than into the ventricular cavity.[2] Ringertz and Reymond[18] found that more than half of their supratentorial tumors were visibly unrelated to the ventricles. Unlike infratentorial ependymomas, those in the cerebral hemispheres often are partly or extensively cystic.

Three histologic forms of ependymoma—cellular, epithelial and papillary—have been defined.[7] Although one architectural type may predominate, most frequently the cellular variety, many of these tumors contain representations of more than one type. In view of this and because of the failure of other investigators[11,18] and ourselves[10] to find any correlation between the histologic varieties of ependymomas and their biologic behavior, we have not classified our cases in this fashion.

There is controversy as to whether papilloma of the choroid plexus is a fourth type of ependymoma or a separate tumor. We

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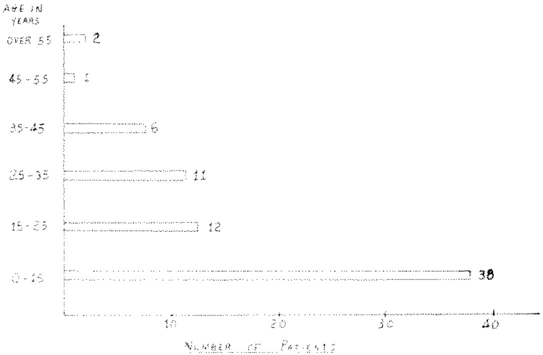

FIG. 1. Diagram showing age distribution of 70 patients with intracranial ependymomas.

recognize choroid plexus papillomas as neoplasms distinct from ependymomas; hence, they are not included in this report.

MATERIAL AND CLINICAL FEATURES

A review of surgical neuropathology records from the Neurological Institute from 1943 to 1960 yielded 65 cases of intracranial ependymomas. Five additional patients seen between 1930 and 1943 were brought to our attention by virtue of autopsy records or tumor recurrence in recent years. Pathologic material was available for review in 63; in the 7 remaining the original pathology report was used. Eighteen had supratentorial and 52 infratentorial tumors. One was lost to follow-up immediately upon discharge from the hospital. The remaining 69 were followed either to the present time or to the patient's death. All were followed for more than 3 years. Fifty-nine patients were available for a follow-up of longer than 5 years. Forty-five of these had infratentorial tumors while 14 had supratentorial tumors. Forty-six were followed for 10 years and 12 for more than 20 years.

AGE

The average age of all patients when first seen was 16.4 years, with a range of 4 months to 66 years. Patients with supratentorial tumors had an average age of 18.8 years, while the average age of those with infratentorial tumors was 15.4 years. Figure 1 shows the age distribution of these patients. Usually, 15 years of age is taken as the dividing line between children and adults; thus, 54 per cent of the ependymomas occurred in the pediatric age group.

SEX

While the total group of tumors was almost equally divided between men and women, 36 and 34 respectively, 12 of the 18 supratentorial tumors were seen in women; 30 of the 52 infratentorial tumors occurred in men.

SYMPTOMS

The average duration of symptoms associated with supratentorial ependymomas prior to diagnosis was 7 months with a range of 2 weeks to 3 years. Symptoms were primarily dependent upon the location of the lesion and usually consisted of headache, seizures and visual disturbance.

Patients with infratentorial tumors most frequently presented with symptoms of increased intracranial pressure such as vomiting, headache or decreased visual acuity. However, nearly one-fifth presented with complaints of either vertigo or loss of balance. The average duration of symptoms in the infratentorial group was 9 months with a range of 2 weeks to 2 years. Of interest is the fact that patients with infratentorial tumors found to be grossly invasive at surgery had symptoms for an average of 5.4 months, whereas patients with tumors which were not grossly invasive had an average symptom duration of 11.0 months.

LOCUS AND GROWTH

All 18 supratentorial neoplasms were grossly related to the ventricular system, but the major growth of 10 was into the cerebral white matter rather than towards the ventricular cavity.

The tumor masses varied in size from 3 cm. to 10 cm. There was not any favored ventricular site of origin, except for a slight predilection for the third ventricle (Fig. 2). Third ventricle ependymomas may be more common than is apparent from these figures, for tumors in this location are frequently treated by a ventricular shunt and irradiation rather than by a direct surgical attack on the tumor.[4]

The 52 infratentorial tumors comprised 74 per cent of the cases in this series. This high proportion of infratentorial ependymomas has been noted by others.[2,8,18] All of the tumors arose in the fourth ventricle. Only 4 tumors were limited to the fourth ventricle at the time of initial exploration; 36 had grown into the cisterna magna. Of these, 16 extended below the foramen magnum into the cervical subarachnoid space; 3 had also grown into the cerebellopontine cisterns. Eighteen tumors appeared grossly invasive as noted by the surgeon; 13 had invaded the cerebellar vermis and/or hemispheres and 5 had invaded the brain stem.

The frequency of seeding from intracranial ependymomas to the spinal subarachnoid space has not been completely clarified. Russell and Rubinstein[19] consider such spread to be a rare event. Svien *et al.*[21] in a study of spinal cords from 19 patients with intracranial ependymomas found subarachnoid implants in 6. None of these had given clinical evidence of their presence. However, others have recorded occasional cases of spinal cord compression from such implants.[23] Seeding has usually resulted from infratentorial tumors that had projected into the cisterna magna. While seeding has often followed operation, this is by no means a necessary precursor.[21] Extracranial spread has rarely been reported following operation.[6,12,15,20,24]

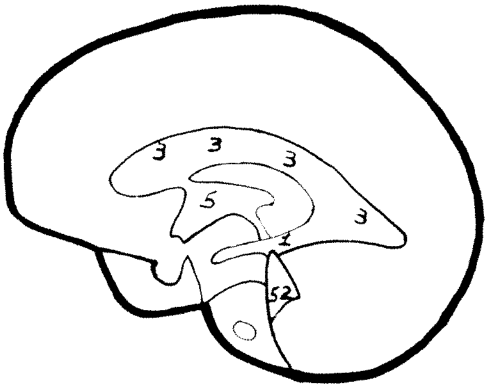

Fig. 2. Diagram showing location of intracranial ependymomas in 70 patients.

Table I

DIAGNOSES OF SURGICAL BIOPSIES—SUPRATENTORIAL TUMORS

Ependymomas		13
Grades I and II	9	
Grades III and IV	4	
Ependymoma with Astrocytoma		0
Ependymoma with Oligodendroglioma		2
Total		15

In this series metastases to the spinal cord were clinically suspected in only 1 patient. A 17 year old boy developed a Brown-Sequard syndrome at the T8 level 6 years after treatment of his primary fourth ventricle tumor. His initial treatment consisted of a partial resection followed by 2,000 r in 13 days to the tumor bed and 2,600 r in 34 days to the entire spinal cord. No autopsy was performed.

Twelve spinal cords from patients who had intracranial ependymomas were examined. In no case was metastasis from the primary ependymoma found.

PATHOLOGIC MATERIAL

Seventy-one surgical biopsies from 63 patients with intracranial ependymomas were reviewed and graded[8] prior to learning the duration of postoperative survival, response to radiation, or the gross characteristics of the tumor (Tables I and II). Our data suggest that those tumors, whether supratentorial or infratentorial, which contain histologic features of increased biologic

Table II

DIAGNOSES OF SURGICAL BIOPSIES—INFRATENTORIAL TUMORS

Ependymomas		41
Grades I and II	26	
Grades III and IV	15	
Ependymoma with Astrocytoma		7
Ependymoma with Oligodendroglioma		0
Total		48

activity (Grades 3 and 4), in general, are more apt to have a poorer prognosis than the more benign appearing tumors (Grades 1 and 2). However, in many instances, the grades correlated very poorly with the subsequent course of the disease and even patients with tumors that were essentially similar had vastly different survival times. We have been unable to find any histologic criteria that would allow one to predict which ependymoma would respond to irradiation and which would not. Consequently, we feel that in most cases the histologic appearance of the tumor is of less importance in estimating prognosis than other factors.[10]

Twenty autopsies were performed on patients with intracranial ependymomas. In 6 patients examined at various times after radiation therapy, there was no evidence of radiation necrosis outside the borders of the tumor. These patients had received 2,000 r to 4,000 r in 3 to 4 weeks.

METHOD OF TREATMENT

Surgery was performed on 65 patients. The surgical procedure usually consisted of a partial resection of tumor with removal of from 10 to 90 per cent of the tumor mass. Where this did not relieve the cerebrospinal fluid block, a shunt was performed. In no instance did the surgeon believe that he had accomplished a total removal of the tumor. In a few instances the patient's condition dictated a more limited procedure. Surgery in these patients was limited to a biopsy and shunting procedure. Twelve had more than one operation. In 8 the secondary procedure was a shunt revision. Four had a second partial removal of tumor from 1 to 10 years following initial operation.

All but one of the patients who did not die in the postoperative period were treated by irradiation. Treatment was started as soon as the operative wound was healed, usually 5 to 10 days after surgery.

Prior to 1953 the method of treatment was basically that formulated by Dyke and Davidoff.[5] This consisted of 2 to 3 short courses of orthovoltage roentgen therapy spaced 1 to 4 months apart. The quality of radiation varied from a half value layer at 0.95 to 1.2 mm. Cu which was obtained by using 200 kv. roentgen rays with 0.5 mm. copper and 1 mm. aluminum added filtration. The target skin distance for all treatments was 50 cm. Patients were treated daily. The quantity of radiation delivered at each treatment was 200 r measured in air.

Generally 3 fields were used. Some patients were treated with 6 or 8 cm. circular ports, while others had rectangular fields ranging in size from 6×6 to 8×10 cm. On some, a combination of circular and rectangular ports was used. The area treated was designed to cover the site of the tumor as determined from roentgenographic and surgical findings. Radiation was given to one or two fields per day.

Since 1953 the method of treatment has consisted of a single protracted course of orthovoltage roentgen therapy. The treatment plan is to deliver a tumor dose of 4,000 r in 4 weeks or 5,000 r in 6 weeks. Children are treated with a modification of Richmond's schedule.[17] Fifty per cent of the adult dose is used for infants of 1 year of age, 75 per cent of the adult dose for children of 5 years and an adult dose for children of 8 years or older. The quality of radiation varied from a half value layer of 1.5 to 3.7 mm. Cu. The greater half value layer was obtained by using 250 kv. radiation with the added filtration of Thoreus II filter. A target skin distance of 50 cm. was used in all cases. Only the tumor site is treated. The size of the treatment fields is similar to those described above.

If there is no evidence of a cerebrospinal fluid block the initial tumor dose is 75 r. This dose is increased by 25 r per day until the patient is receiving a daily tumor dose of 165 r to 200 r.

Patients with increased intracranial pressure are more difficult to treat, for the initial reaction to radiation frequently further elevates the already high intracranial pressure. The initial treatment varies from 25 r to 50 r tumor dose depending on the patient's condition. This is increased by 25 r each day to a tumor dose of 165 r to 200 r daily. Careful clinical assessment of the patient's status is of utmost importance. Any changes that indicate increasing intracranial pressure necessitate a further protraction of the radiation build-up. Occasionally, treatment will have to be discontinued and surgical decompression by a shunting procedure performed before adequate radiation therapy can be given.

Patients with radioresponsive tumors usually show clinical improvement by the end of the course of therapy. It is not unusual for patients destined to have a good result to complain of morning nausea and vomiting for up to a year after treatment. This should not be misinterpreted as indicating a failure of treatment or a recurrence of tumor.

Patients were retreated as the need arose. The retreatment tumor dose was usually 1,800 r to 2,000 r in from 2 to 3 weeks. One patient received a total tumor dose of 8,000 r in 10 years, and another 16,000 r in 14 years. In neither of these cases was there any clinical evidence of radiation damage to the central nervous system.

Some authors[5,9,13,14] recommend that ependymomas be treated in the same manner as medulloblastomas, *i.e.*, radiation therapy to the entire central nervous system axis. Bouchard and Peirce[1] do not advocate prophylactic treatment of the spinal cord. Only 4 of our cases were so treated. Interestingly enough, one of these treated cases was the only patient in the series to develop a spinal cord implant from his primary disease.

Table III

RESULTS OF OTHERS

1. Ringertz and Reymond,[18] surgery
   Supratentorial Tumors—21 patients: 15 per cent 5 year survival; average survival, 2 years
   Infratentorial Tumors—33 patients: 50 per cent operative mortality; 17.5 per cent 5 year survival; average survival, 13 months
2. Bouchard and Peirce[1] (12 cases), surgery and radiation therapy
   75 per cent 3 year survival
   58 per cent 5 year survival
   50 per cent 10 year survival

Table IV

PATIENTS STILL ALIVE

Years Surviving	No. of Patients
< 3	2
3–5	3
5–10	2
>10	7
	—
Total	14

RESULTS OF TREATMENT

Ringertz and Reymond[18] report a follow-up of 54 patients with intracranial ependymomas (21 supratentorial and 33 infratentorial), who were treated by surgery alone. The supratentorial group had local recurrence in 7 of 21 patients. The 5 year survival rate was 15 per cent and the average survival was less than 2 years. The infratentorial group had a 50 per cent operative mortality. The remaining 15 patients had 6 local recurrences. The overall 5 year survival rate was 17.5 per cent, or 35 per cent of those surviving surgery. The average survival was 13 months (Table III).

Bouchard and Peirce[1] reported 12 ependymomas that were treated by surgery and irradiation. Seventy-five per cent of these patients were alive after 3 years, 58 per cent were alive after 5 years and 50 per cent after 10 years (Table III).

In our series 4 patients died before any type of treatment could be started and 13 patients died postoperatively. We have considered any death occurring within 1 month of surgery as a postoperative death. Thirty-six patients succumbed to local recurrence of tumor. One died of spread to the thoracic spinal cord and 1 died of bronchogenic carcinoma. Fourteen patients are still alive at the time of this report (Table IV).

The average survival from time of diagnosis was 5.2 years with a range of 1 month to 26 years. Patients with supratentorial tumors survived an average of 2.8 years,

TABLE V

SURVIVAL FROM TIME OF DIAGNOSIS

Infratentorial Tumors		Supratentorial Tumors	
Years Surviving	No. of Patients	Years Surviving	No. of Patients
< 1	52(7)	< 1	18(6)
1–3	36	1–3	11
3–5	19	3–5	6
5–10	15	5–10	2
>10	13	>10	1

The number of operative deaths included are noted in parentheses.

whereas those with infratentorial tumors survived an average of 6 years. If one eliminates postoperative deaths, the average survival is 3.7 years and 7 years respectively (Table v).

Fifty-nine patients were followed for a 5 year period from the time of diagnosis. Seventeen, or 28 per cent, were alive at the end of that time. If postoperative deaths and untreated cases are eliminated the 5 year survival rate is 41 per cent. Thirty-three per cent of patients with infratentorial tumors and 14 per cent with supratentorial tumors survived more than 5 years. Eliminating postoperative deaths, the per cent surviving increases to 45 and 22 per cent respectively (Table vi).

Of the 36 children in this report, only 9, or 25 per cent survived longer than 3 years. Fifteen of 33 adults, or 45 per cent, survived longer than 3 years.

It is of interest that 7 patients who survived for more than 10 years subsequently died of local recurrence of tumor. One patient was asymptomatic for 24 years following initial surgery and minimal radiation (900 r) only to die of local recurrence of posterior fossa tumor.

Survival of itself is of little value. It is only worthwhile if the patient is a useful individual. The functional state of patients surviving for more than 1 year following treatment was carefully evaluated and the patients were divided into 4 groups: (1) Excellent. Patient asymptomatic. Neurologic examination negative or only minimal deficit elicited by the examiner. (2) Good. Mild neurologic deficit, but patient functions well. (3) Fair. Moderate neurologic deficit. Patient's activities are curtailed, but he can do limited work and is capable of partial self-care. (4) Poor. Severe neurologic deficit. Needs care from others. The functional state of patients surviving more than 1 year is shown in Table vii. As can be seen, patients with infratentorial tumors were considerably more intact than patients with supratentorial disease.

Two illustrative case reports are presented in brief to document the value of radiation therapy in some patients with intracranial ependymoma, particularly to emphasize the value of retreatment when symptoms of recurrence appear.

ILLUSTRATIVE CASES

Case No. 839039. An 18 year old boy was admitted to the Neurological Institute with a 24

TABLE VI

FIVE YEAR SURVIVAL FROM TIME OF DIAGNOSIS

	No. Followed	No. Surviving	Per Cent Surviving
	5 Years	5 Years	
All Cases	59	17	28
All Surviving Surgery and Receiving Radiation	41	17	41
All Infratentorial Tumors	45	15	33
Infratentorial Cases Surviving Surgery and Receiving Radiation	33	15	45
All Supratentorial Tumors	14	2	14
Supratentorial Cases Surviving Surgery and Receiving Radiation	9	2	22

month history of vomiting, headache and dizziness. A suboccipital craniotomy was performed and a 5 cm. mass was found filling the fourth ventricle and obstructing the aqueduct of Sylvius. Approximately 20 per cent of the tumor was removed and the obstruction to the cerebrospinal fluid pathway was relieved. Postoperatively, he received two short courses of radiation therapy for a total estimated tumor dose of 2,500 r to the posterior fossa in 2 months. Twelve years later he developed severe headaches and ataxia. An estimated tumor dose of 1,500 r in 3 weeks was given to the posterior fossa. His symptoms cleared several days following completion of therapy. Three years later he was readmitted with headache and mild ataxia. He received 700 r in 2 weeks to the posterior fossa and again his symptoms cleared. He returned approximately 1 year later complaining of marked gait difficulty and vertigo. He was retreated with 1,000 r in 3 weeks to the posterior fossa with no apparent response and died 7 months later, approximately 16 years from his initial treatment.

Case No. 277121. A 20 year old man was admitted to another institution with a 6 months' history of vomiting. A suboccipital craniotomy was performed and a 4 cm. mass was found to fill the fourth ventricle. Nearly all of this was removed and the obstruction to the cerebrospinal fluid pathway was relieved. Postoperatively, he was treated with an estimated tumor dose of 3,000 r in 21 days to the posterior fossa. Six years later he was admitted to the Neurological Institute complaining of imbalance and vomiting. These symptoms cleared completely following an estimated tumor dose of 2,000 r in 14 days to the posterior fossa. Two years later he returned complaining of headache and vomiting. Another tumor dose of 2,000 r in 14 days was administered to the posterior fossa, and again his symptoms cleared completely. One year later he returned complaining of gait imbalance. This time a tumor dose of 2,500 r in 20 days was given to the posterior fossa, and once again his symptoms cleared. Three years later he again returned complaining of imbalance. Symptoms cleared following a tumor dose of 1,500 r in 10 days. One year later he returned complaining of imbalance and dysarthria. He was re-explored. A small amount of tumor was removed and a ventriculopleural shunt was performed. Postoperatively, he received a tumor dose of 3,300 r in 23 days to the posterior fossa. He improved only moderately and gradually went downhill and died 3 years later. This patient survived a total of 17 years.

Table VII

FUNCTIONAL STATE OF PATIENTS SURVIVING MORE THAN 1 YEAR FROM TIME OF DIAGNOSIS

Condition	No. of Patients	No. of Patients
	Infratentorial Tumors	Supratentorial Tumors
Excellent	13	3
Good	14	2
Fair	5	4
Poor	3	1

DISCUSSION

The 5 year survival rates in this series are better than those reported by Ringertz and Reymond[18] in their group of patients who were treated by surgery alone. Furthermore, the high operative mortality in their series may have eliminated many advanced cases which would have further lowered their survival figures (Table III). In our study there was no significant difference in the survival of patients treated by the multiple course method compared with those treated by a single protracted course irradiation. However, a survey of the patients' clinical records seemed to indicate that patients receiving a single protracted course of treatment had a quicker regression of symptoms and more frequently completed a full course of therapy than those treated by multiple series. We see no need to abandon the present mode of treatment.

There seems to be a great variation in the response of ependymomas to radiation. Some patients were aided remarkably by radiation therapy; others did not receive any apparent benefit. The reasons for this are unknown. We could find no histologic or clinical criteria which would allow one to predict which ependymoma will respond to radiation therapy and which will not. Therefore, we believe that all patients with intracranial ependymomas should have postoperative radiation therapy to the site of the tumor.

TABLE VIII

DEFINITION OF SURGICAL STAGE OF INFRATENTORIAL EPENDYMOMAS

T1	Tumor limited to 4th ventricle
T2	Tumor has extended outside the 4th ventricle into, but not beyond, the cisterna magna
T3	Tumor has extended beyond the cisterna magna; the usual extension is to the cervical subarachnoid space, but may be to the cerebellopontine cisterns
T4	Tumor is grossly invading the cerebellum or brain stem regardless of the size of tumor
M	Distant metastases

Patients whose tumors have shown a good response to initial treatment should be retreated with a tumor dose of from 1,500 r to 2,000 r whenever symptoms warrant. The danger inherent in regrowth of tumor is far greater than that of damage to the normal brain from repeated radiation treatments.

In this study none of the 12 spinal cords examined at autopsy showed any evidence of a metastatic implant. This is in marked contrast to the group of Svien *et al.*,[21] wherein 6 of 19 spinal cords showed metastatic deposits. Only 1 patient in our series of 70 cases had clinical findings suggestive of a spinal cord metastasis from an intracranial ependymoma. None of the 19 patients of Svien *et al.*[21] had any clinical findings to suggest spinal cord disease.

Although there is room for argument regarding the true incidence of spinal cord implants, there seems to be no question that clinically significant spread is quite rare. Inasmuch as the rationale for treatment must be based upon clinical findings and not on autopsy data, we see no reason for treating the entire central nervous system axis as a prophylaxis for possible spinal cord metastases.

The prognosis of a patient with a slowly growing supratentorial tumor such as an ependymoma is to a large degree influenced by the location of the tumor. The duration of symptoms as well as the resectability of the tumor varies greatly depending upon the site of the lesion. An attempt to correlate survival with various parameters is subject to considerable error.

Infratentorial ependymomas, on the other hand, all arise in a common location; thus it is possible to attempt to correlate survival with pathologic-clinical parameters. The duration of symptoms prior to seeking medical aid probably reflects, in large part, both the rate of tumor growth and its invasiveness. There is a good correlation between duration of symptoms and survival of patients with infratentorial ependymomas. Generally, the longer the duration of symptoms prior to diagnosis, the longer the survival.

The cure rate of many tumors outside the nervous system has been related to clinical or operative staging based primarily upon the local extent or invasiveness of the tumor. In most cases such staging has been shown to be superior to histologic grading as a means of predicting survival.[3,15] It has been possible for us to divide infratentorial ependymomas into groups representing the extent of the neoplasm (Table VIII). The classification of infratentorial ependymomas in this manner offers a more reliable estimate of prognosis than any clinical or pathologic criteria. A study of factors influencing the prognosis of intracranial ependymomas is the subject of another publication.[10]

CONCLUSIONS AND SUMMARY

Seventy case records of intracranial ependymoma have been reviewed. This tumor occurs most frequently in young people; slightly more than one-half of the patients in this series were children.

The prognosis is worse in children than in adults. Patients with supratentorial tumors have a poorer prognosis and generally have greater neurologic deficit than do patients with infratentorial ependymomas.

Surgery followed by radiation therapy to the tumor site offers a greater chance of cure than surgery alone. Retreatment of a recurrent tumor may add many useful years to the patient's life. There is no valid reason to subject the entire central nervous system axis to prophylactic irradiation.

There appears to be a direct relationship between the duration of symptoms prior to surgery and the survival of patients with infratentorial ependymomas. This would suggest that the rate of tumor growth or its invasiveness greatly influences survival. Surgical staging of infratentorial ependymomas based on their extent and invasion of surrounding brain is the most valuable prognostic criterion available. We propose that all posterior fossa ependymomas be classified in this manner.

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AN AFTER-LOADING SYSTEM UTILIZING CESIUM 137 FOR THE TREATMENT OF CARCINOMA OF THE CERVIX*

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IT IS axiomatic that for many a radiation therapist, fulfillment cannot be realized until he has designed his own applicator for the treatment of carcinoma of the cervix. Happily, the vagina, even in a diseased state, will accommodate an almost infinite variety of shapes and configurations of devices, and, *provided good clinical judgment is used and radiation dosimetry is carefully planned*, the radiotherapist can indulge his whims and fancies for ovoids, cylinders, kidney shapes, boxes, "colpostats," ratchets, springs, spacers, detachable handles, etc., in the knowledge that by so doing he does not jeopardize the patient's chances for cure. Few claims are made that any individual applicator has anything to do with the cure rate for cervical cancer; it is generally agreed, however, that radiation dosimetry is of paramount importance in this regard. A review of results reported from major centers in America and other parts of the world[17,32] reveals a trend towards improved survival and decreased morbidity over the last 2 to 3 decades, due in part to technical improvements in therapy. The over-all 5 year cure rates now reported vary between 35 per cent and 50 per cent, and despite the fact that treatment techniques may be widely different, no clear advantage is apparent for any particular method of treatment.[17] Such differences as exist in reported cure rates are certainly attributable to factors other than the type of radium applicator used: they may be related to the quality and selection of case material, to minor differences in clinical staging from one institution to another and to varying degrees of experience and clinical judgment amongst those treating the disease.

A glance through a catalog from one of the radium equipment companies* discloses that at least 17 different types of cervix applicators are offered for sale. Many are modifications of the Paris and Manchester applicators. No doubt other contrivances that have been described are available from other agencies or may be obtained by special order. Many more applicators have been "home-made" by their inventors or built in hospital workshops. It would be conservative to guess that there are more than 40 different types and modifications of cervical applicators in regular use at the present time throughout the world. Since the superiority of one piece of equipment over another is technical rather than therapeutic, and since there are a great number and variety of appliances already available, the introduction of yet another system needs considerable justification.

THE CESIUM 137 AFTER-LOADING SYSTEM

The merits of the system to be described can be summarized as follows:

1. *Simplicity and Immediate Availability.* The applicator (or outer shell) is inexpensively constructed of semi-soft vinyl plastic (polyvinyl chloride, PVC); it is pre-packed, sterilized and ready for immediate use at any time. It is used only once and discarded. There is, therefore, nothing to

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prepare, nothing to clean up and nothing to be put away after use.

2. *Flexibility*. The applicator is designed to adapt to almost any anatomy, large or small. It can be used where there is vaginal narrowing or distortion by simply paring it down to size and shape with a scalpel or scissors, since, in any event, it is disposable. It can, in fact, be "custom tailored" to the neoplasm. The actual design of the equipment described herein is quite arbitrary and represents a compromise between the writer's prejudices (H.H.) and the financial resources available to him for development. The applicator is modeled on the Paris type but its configuration could be changed in almost any way without detracting from the over-all principles of the treatment system. If desired, the applicator could be constructed to give a set of constant reproducible geometric arrangements as preferred by some workers.[9]

3. *Minimization of Radiation Exposure to the Operator*. The device is "after-loaded"; it is also (if the term is allowable) "before-unloaded." Specially designed sealed cartridges* containing Cs^{137} sources are permanently kept within a mobile lead safe which need only weigh about 100 pounds, and which serves both as storage unit and transport unit. Exposure to the radiation therapist and other personnel is considerably reduced by virtue of the mobility of the cesium safe; in fact, exposure associated with handling and transportation of inadequately protected radioactive sources[7,43,45] is eliminated. The operator handles the sources for a total time of about 2 minutes (loading into and unloading from the applicator within the patient) and both of these operations are performed at the bedside. Since there is no radiation exposure in the operating room, there is no need for any special protective equipment[41] in this area.

More subtle marginal advantages accrue from the after-loading principle. Firstly, the outer shell can be inserted into the patient at the time of the initial biopsy and examination under anesthesia before histologic confirmation of the disease is available. As soon as malignancy has been confirmed the device can be loaded with the radioactive sources. Secondly, where there is a difference of opinion between the gynecologist and the radiotherapist as to which of them should carry out the intracavitary therapy, "after-loading" allows for a division of labor, whereby the gynecologist can insert the device (outer shell) and the radiotherapist can prescribe and carry out the actual treatment by inserting and withdrawing the radioactive sources. Since most gynecologists are familiar (or can become so) with the simple principles involved in positioning intracavitary devices, this division of labor arrangement could prove highly satisfactory in situations where it is appropriate.

4. *"Customized" Dosimetry*. The present system lends itself either to individualization of treatment or to a standard universally applicable system of dosimetry. A number of different radioactive source loadings are available and if required, loadings can be biased to one side or the other. In addition, sources can be changed at any time during the course of treatment or withdrawn after different time periods without disturbing the applicator. Thus it is possible after the beginning of treatment to revise the whole dosimetry, to fractionate or to bias the dose in any desired fashion. On the other hand, if a standard type of dosimetry is required, this presents no difficulty.

5. *Elimination of Cleaning, Sterilizing and Other Manipulation of the Source Cartridges*. The cartridges, when in use, are completely enclosed within the applicator and thus do not come in contact with the tissues of the patient. They should never get soiled except accidentally, do not require sterilizing, and should not need to be opened or otherwise manipulated over a period of many years. Special provision need not therefore be made for heat or

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* Throughout this paper the word "cartridge" refers to a permanently sealed assembly containing one or more radioactive sources.

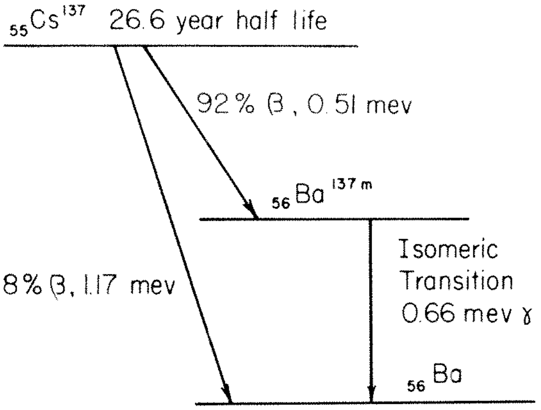
$_{55}Cs^{137}$ 26.6 year half life
92% β, 0.51 mev
$_{56}Ba^{137m}$
Isomeric Transition 0.66 mev γ
8% β, 1.17 mev
$_{56}Ba$

Fig. 1. Energy level diagram for cesium 137 decay.

steam sterilization[10] or for "cold" sterilization (which is never quite satisfactory). There is in fact little or no use for a Radium Room in so far as cervical intracavitary treatment is concerned.

6. *Easy and Effective Radiation Protection.* The use of cesium 137 (as opposed to radium or cobalt 60) simplifies the problems of radiation protection both inside and outside the patient, without in any way compromising the treatment. Whole body dose to the patient is slightly less with cesium 137, especially if lead shields are incorporated in the applicator. This and other aspects of protection for cesium 137 will be discussed in more detail below.

ADVANTAGES OF CESIUM 137 FOR INTRACAVITARY USE

Cesium 137 is an abundant fission product. It is inexpensive and is obtainable in a highly purified form.[1] Methods have been developed for physically trapping the isotope in a chemically inert medium[5,14,18,19,35,40] and thus former problems of containment of Cs^{137} due to its peculiar physical characteristics and its tendency to leach, have now been overcome. The decay scheme for Cs^{137} is shown in Figure 1. The beta emissions are 99 per cent absorbed by an 0.5 mm. stainless steel wall (which is used for source encapsulation); only the monoenergetic 660 kev gamma rays are utilized for therapy.

The long half life of Cs^{137} (for present purposes this is taken to be 26.6 years*) compares favorably with that of Co^{60} (5.3 years) which is its closest artificially produced radioisotope rival for intracavitary use. It is estimated that the useful life of a set of Cs^{137} sources is in the neighborhood of 16 years, at which time some of them will need to be replaced. Using Cs^{137} sources, a treatment which originally requires a 5 day application, would, using the same sources 16 years later, require approximately a 7½ day application. A time correction chart for a 16 year period is shown in Figure 2. At the end of some arbitrary time, say 10–15 years, a set of sources can be brought back to about their original level of activity by exchanging those of lower denomination for new high activity sources.

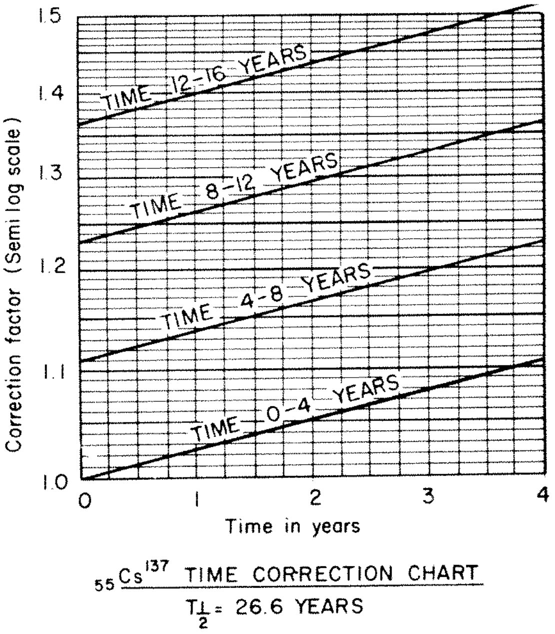

Fig. 2. The activities of a set of Cs^{137} sources are expressed in "mg. radium equivalent." For clinical purposes, the dose is calculated as for radium, but in order to allow for the slow decay of Cs^{137}, the calculated time of application must be increased somewhat according to the age of the sources. After 4 years, for instance, the time of application must be increased by a factor of approximately 1.1.

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* Radiological Health Handbook, U. S. Department of Health, Education and Welfare, Washington 25, D. C., Sept. 1960 p. 333.

TABLE I

COMPLETE SET OF CESIUM 137 SOURCES FOR AFTER-LOADING CERVIX APPLICATOR

Source Size mg. Ra equivalent	5	10	15	20	Total
mc Cs^{137} (approx.)	12	24	36	48	
Number required	16	10	2	2	30
Total mg. Ra equivalent	80	100	30	40	250
Cost (approx.)	$1,184	$760	$180	$184	$2,308

Total Amount of Cs^{137} = 600 mc (approx.).
Approximate Cost of Equivalent Amount of Radium (250 mg.) in suitable Units = $5,500.00.

The initial cost for a complete set of sources for treatment of cancer of the cervix is about half the cost of a similar set of radium sources (Table I). Radium is, of course, more permanent, but radium sources may occasionally require re-encapsulation and re-calibration at considerable cost. Radium will only become more economical than cesium 137 after about 40 years. However, it is difficult to anticipate the requirements for intracavitary treatment of carcinoma of the cervix 40 years hence.

Small amounts of lead incorporated in the applicator will provide good attenuation of the 660 kv. gamma rays and thus worthwhile protection for the rectum or bladder if this is desired (Fig. 18). A lead disk 1 cm. in diameter and 5 mm. thick represents almost 1 half value layer for cesium 137 gamma rays and adds little weight to the applicator. Protection outside the patient for nursing personnel, etc. is similarly very effective. Methods for protection in the wards for radium have been well described[7,8,26,48] and similar principles are used to much greater advantage for cesium 137. It can be calculated from available data[2] that a bedside lead screen 1 inch thick (Fig. 3) will transmit about 6 per cent of the cesium 137 gamma rays as compared with about 22 per cent of radium gamma rays. Actual measurements around the bedside of patients show that the screen is, for practical purposes, about twice as effective for cesium 137 as for radium, partly because of the contribution of scatter to the measured values (Fig. 4 and 5). A Jordan Model AGB-10KG-SR Survey Meter was used for these measurements.

Storage and transportation of Cs^{137} sources is extremely simple. The permanent storage unit for about 700 mc of Cs^{137} need not weigh more than 100 pounds and serves also as a transport unit for wheeling to the patient's bedside (Fig. 13). Some data concerning the transmission in lead for radium and cesium 137 gamma rays are shown in Figure 6.

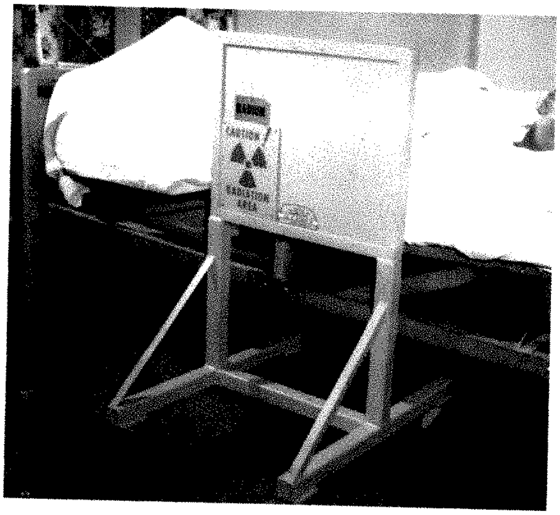

FIG. 3. The lead screen is 24 inches long, 20 inches high and 1 inch thick. Together with the supporting frame and casters, it weighs about 250 pounds, but is quite easy to move. It is constructed so that an extra thickness of lead could be added if required; however, for Cs^{137} the 1 inch screen gives excellent protection (see Figure 5 and text).

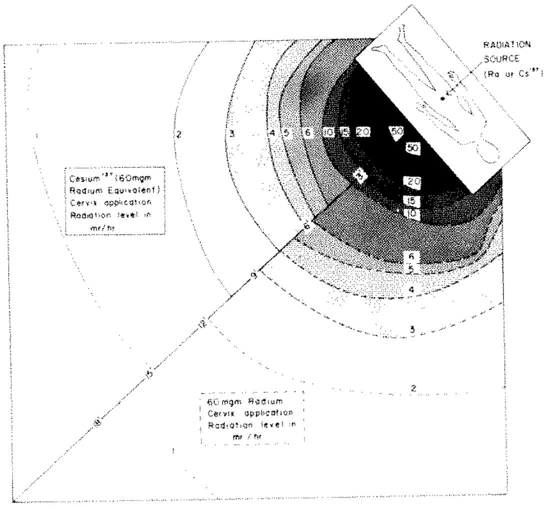

Fig. 4. A comparison is shown of the levels of radiation for 60 mg. radium and the equivalent amount of cesium 137 around the bed of a patient undergoing intracavitary therapy for carcinoma of the cervix. The measurements were made using a masonite phantom. The distance from the patient in feet is indicated on the diagonal line.

Cesium 137 sources are intrinsically safer than similar radium sources and do not entail many of the hazards associated with the latter.[13] There is no radon inhalation hazard and since the Cs^{137} containing material (see below) is of considerable density and has no tendency to become airborne, there is little risk of inhaling the radioactive material itself. Helium gas buildup can occur within radium capsules and may be responsible for their rupture;[36] there is no alpha emission from cesium 137. The Cs^{137} is combined in a ceramic material (see below) and in the event of a "spill" due to breakage of a capsule, contamination is comparatively easy to deal with, since the Cs^{137} is trapped within a dense inert powder of large particle size. Even in the unlikely event that the material is ingested, it will not be absorbed or metabolized and is eliminated in the stools.[33] Thus, the widespread contamination which is known to occur when a radium capsule ruptures due to its contents becoming airborne is not a problem with Cs^{137} incorporated in ceramic. Radium contamination, on the other hand, may be extremely difficult and enormously expensive to clean up.[13]

THE AFTER-LOADING PRINCIPLE

The principle of after-loading is no longer new.[3,22,23,24,25,37,38,42,44,46,47] One of its main purposes is to reduce radiation exposure to the operator. Basically, it consists of the introduction into the tissues or the body cavities of an inactive "shell" or set of guides which can be positioned with care and precision, and into which the radioactive sources can be speedily loaded at a later time. The advantages of this technique are obvious. The sense of urgency in the operating room, due to handling of "hot" sources, is eliminated. Loadings can be precalculated at leisure based on roentgenograms of the empty applicator in the patient, and can be customized to the tumor. Handling time for the radioactive sources is reduced to a minimum. Ideally, there should be no need to prepare or load source carriers before the procedure and no need to unload or to disassemble them afterwards.

To be logical, the after-loading concept is not fully exploited unless some attention is given to "before-unloading" in order to avoid the considerable amount of work that may be involved and the radiation exposure that may be incurred when a radioactive

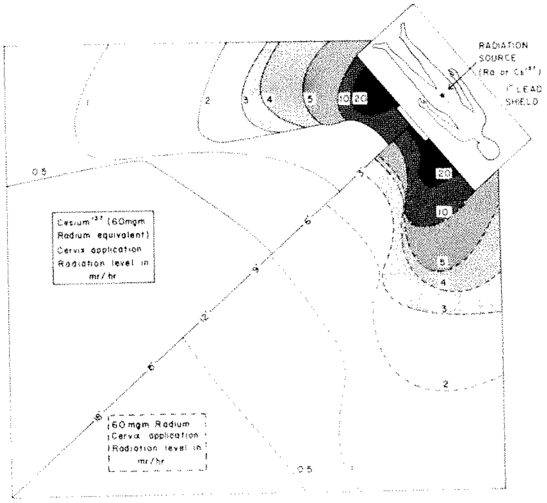

Fig. 5. The situation is the same as in Figure 4; however, a 1 inch lead screen is placed at the bedside. The measured values indicate that the screen gives about twice as much protection for cesium 137 as for radium. This is less than might be anticipated, but scatter contributes considerably to the radiation levels in the "shadow" of the screen.

device is removed from a patient, disassembled and the sources cleaned or soaked and subsequently put away in the safe. It should, therefore, be as easy to withdraw the active sources from the applicator within the patient as it is to insert them, and if they have not been soiled or contaminated in use they can be transferred directly from patient to storage safe without any additional handling. The empty "shell" can then be unhurriedly removed from the patient, and if disposable, there is nothing to clean, sterilize or prepare for subsequent use.

THE CESIUM 137 SOURCES

Cesium 137 is in the form of "3M Radiating Microspheres."* Grossly this material appears as a milky white powder (Fig. 7) and microscopically as small spherical particles (Fig. 8). The microspheres are available in carefully graded sizes from 10–150 microns and above, but for most purposes the 50–60 micron size is used. They are physically insoluble in almost all organic and inorganic solvents, including concentrated acids or alkalis. Aqua regia at 100° C. or higher has little effect on the material,[33] and less than one part per billion is soluble in salt water or dilute acid. The absolute density of the microspheres is 3 gm./cc. (bulk density about 2 gm./cc.) and the melting point is 1,500° C. The radiation stability is such that doses in excess of one billion rads cause no visible change and no decrease in the retaining power of the ceramic material for isotopes. Leaching is, for practical purposes, negligible.[33]

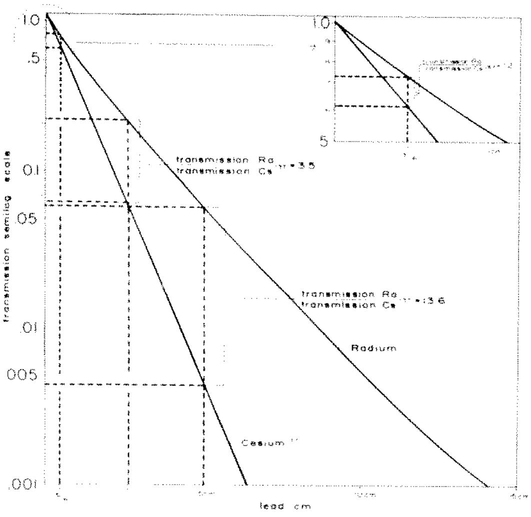

Fig. 6. A comparison of transmission of radium and cesium 137 gamma rays in lead is shown (adapted from data by C. B. Braestrup and H. O. Wyckoff, published in 1958[2]). The three thicknesses chosen as examples are: 3/16 inch representing the lead shield within the applicator for the protection of the rectum or bladder (top right), 1 inch representing the thickness of the bedside lead shield and lead screen, and 5 cm. representing the minimum wall thickness for the cesium 137 storage safe.

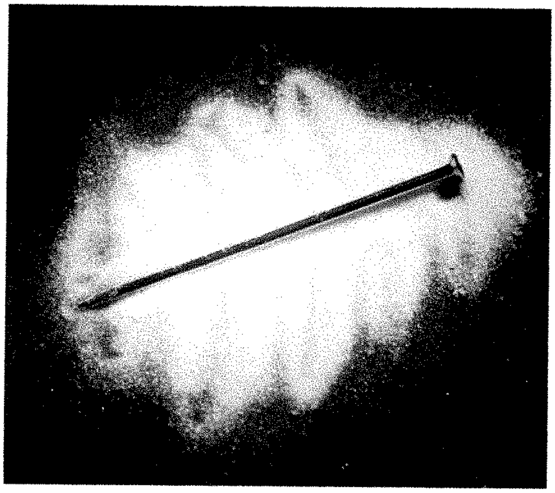

Fig. 7. "3M Radiating Microspheres." The material, which for present purposes incorporates Cs^{137}, is a coarse heavy powder. A 1 inch domestic pin is shown for comparative size.

A great variety of isotopes can be incorporated in the microspheres at almost any desired level of activity and the experimental and clinical uses for these unique isotopic materials are now being explored.[15,20,31,40,51] Specific activities for Cs^{137} up to 10 c/gm. of ceramic are possible, and thus the material is ideally suited for use in needles and tubes for interstitial and intracavitary therapy.

The sources developed for the cervix treatment system are all of standard size and shape (Fig. 9). They are cylinders of external length of 1 cm. and of external diameter of 3 mm. The construction and

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* Minnesota Mining and Manufacturing Company, Nuclear Products Division, St. Paul, Minnesota.

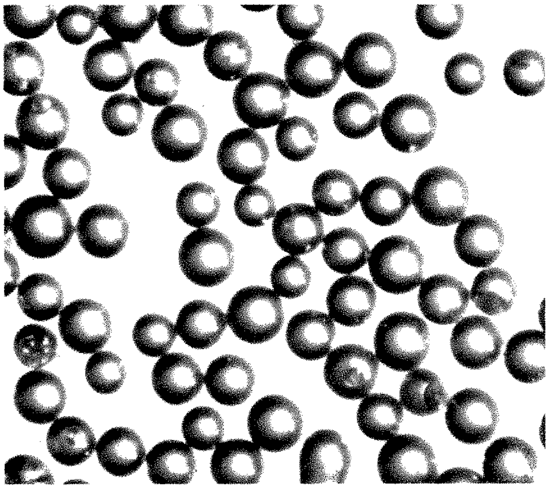

FIG. 8. Photomicrograph of the ceramic microspheres. When used as described in the text, the particles are about 50 microns in diameter.

dimensions of the sources are shown in Figure 10. The ceramic microspheres occupy a cylindrical volume 6 mm. long by 2 mm. diameter at the geometric centers of the sources. A stainless steel plug seals the capsule and is soldered in with a silver brazing alloy.

The sources are contained in long flexible cartridges of different loadings. The sources are arranged longitudinally at the distal ends of the cartridges, in some cases separated by hollow stainless steel balls which act as spacers (Fig. 11). The major length of the cartridge consists of automobile speedometer cable (which has been found to give about the right degree of flexibility) and the outer enclosure is a braided metal mesh tubing of the type found in electrical cable. There is a short stainless steel rod, or handle, at the inactive end which carries a code of grooves radiologically visible, and in addition carries a color code, which identifies the Cs^{137} loadings within each cartridge. A total of 5 such cartridges of identical over-all length gives a selection of different loadings (from 20 mg. to 60 mg. radium equivalent) and different active lengths (from 2 cm. to 9.5 cm.) to correspond with different lengths of uterine cavity. There is also a choice of 15 mg. or 20 mg. radium equivalent sources at the tips of slightly shorter cartridges for the vaginal portion of the applicator (Fig. 12).

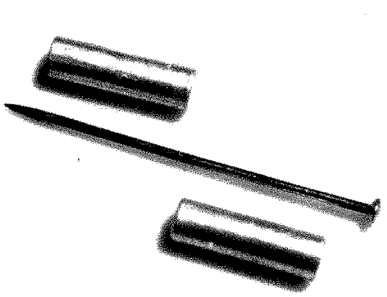

FIG. 9. The external appearance of two cesium 137 sources is shown together with a 1 inch domestic pin. They are of stainless steel, 1 cm. over-all length and 3 mm. outside diameter.

The 9 cartridges required for the treatment system are assembled by the source manufacturers and are not again disturbed or disassembled until such time as they have decayed below useful values. Together with the mobile storage safe, they form the *only permanent part of the treatment system.* The cartridges slip very easily in and out of the disposable plastic applicators which are positioned in the patient.

The lead safe is shown in Figure 13. It is designed to accommodate the total of 9 cartridges and is basically a solid cylindrical block of lead about 6 inches in diameter cast in a stainless steel outer tube. The center of the cylinder is drilled longitudinally to accommodate the 9 cartridges. The lid is fitted with a lock; the unit is mounted on a small cart on casters and is very easy to move about. Lock-up storage space is provided on the cart for handling instruments, such as long-handled forceps, etc. The dose rate at the surface of the cart (when it is fully loaded with 750 mc of Cs^{137}) is less than 3 mr per hour. In order that the design and manufacture of the safe would be as simple as possible and in order that radiation protection would be more than adequate, generous amounts of lead were used and the safe was found finally to weigh 150 pounds. With refinements in design it should be possible to reduce this weight to something less than 100 pounds.

THE DISPOSABLE PLASTIC APPLICATOR

It is emphasized again that the design of the applicator is arbitrary. For the equipment to be described, we have adapted the basic shape of the Paris vaginal colpostat for after-loading. It was not considered necessary to evolve an entirely new design, nor to attempt to reproduce in plastic any of the more complex applicators, although this could have easily been accomplished by molding processes. The applicator we have developed is made from the following inexpensive and universally available components: 5 pieces of vinyl* tube (2 different sizes); 10 small disks of vinyl (3 different sizes); 3 short vinyl rods; 8 lead disks, ½ inch diameter, 3/32 inch thick (sometimes not used); and 2 specially shaped steel springs (sometimes not used).

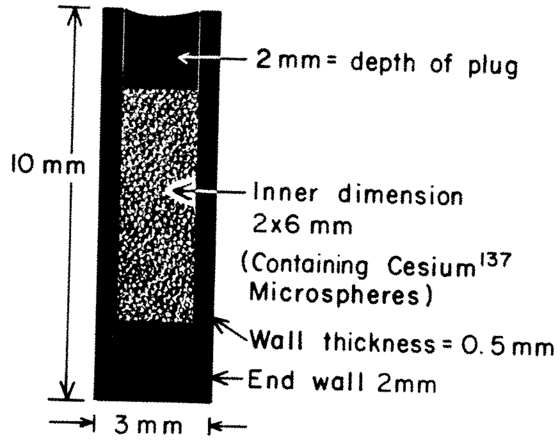

Fig. 10. Construction of cesium 137 sources. The capsule is made of stainless steel and the plug is sealed with silver brazing alloy. Since very high specific activities are obtainable in the ceramic microspheres, almost any level of activity that could conceivably be required for intracavitary use can be contained within the small inner cylindrical volume.

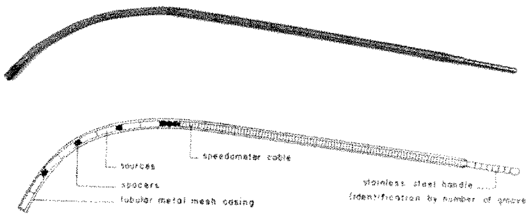
sources
spacers
tubular metal mesh casing
speedometer cable
stainless steel handle
(identification by number of grooves)

Fig. 11. Typical source "cartridge" (intrauterine type). The whole unit we have called a "cartridge." The word "source" is reserved for the 1 cm. long stainless steel cylinder containing the radioactive material. The appearance and inner construction of a typical cartridge are shown. The unit is permanently sealed so that sources cannot be removed. The over-all length of all cartridges for intrauterine use is 11 inches and those for intravaginal use 8½ inches. The speedometer cable makes the whole unit very flexible in every direction. The construction allows for recovery of the original straight form and will not allow the sources to come out of alignment within the cartridge. At its distal end, the cartridge is extremely flexible and can be bent sharply to a right angle or more. In addition to the code of grooves on the handle, a color code is also used for identification purposes.

The value of the components is negligible; however, the actual price of an assembled applicator, which is based mainly on tooling and labor costs, will depend on the quantities produced. If 100 complete applicators are specially manufactured from the above components, the price per item works out at about $2.50. Mass production would considerably reduce this figure, which, in any case, is quite trivial in relation to the over-all cost to the patient or to the institution of an intracavitary treatment for carcinoma of the cervix.

Figure 14 shows the assembled applicator. It is normally packaged in a sealed polyethylene bag, or in some form of sterilizer tubing such as "Weeck" tubing or "Rapitube" and is best sterilized by ethylene oxide gas. The central uterine tube, because of its wall thickness, will adapt to different positions and flexions of the uterus without occlusion or appreciable loss of lumen due to kinking. Even when this tube is flexed at a right angle, the cartridge containing the sources will readily negotiate the bend without binding or jamming. If desired, this central tube can be made of a more rigid material which, when inserted, will tend to hold the uterus in a more verti-

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* Polyvinyl chloride (PVC).

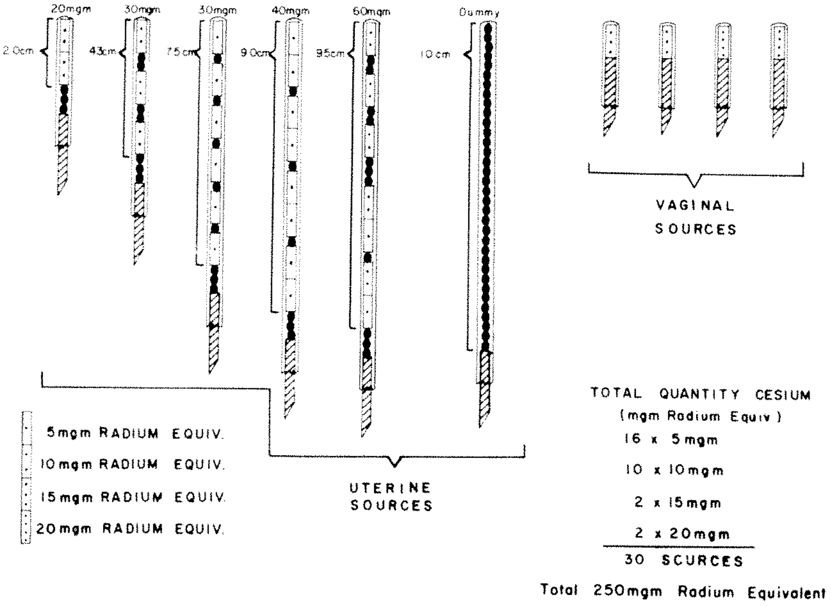

Fig. 12. Cesium 137 sources for treatment of carcinoma of the cervix (after-loading applicator). The construction of the complete set of cartridges is shown diagrammatically. Each rectangular box represents a cylindrical source of outside measurements 1 cm. long and 3 mm. in diameter. The amount of radioactivity in each source is coded in this diagram by a system of dots. The large black spots within the cartridges represent hollow stainless steel balls acting as spacers (bead chain). The hatched areas represent speedometer cable. Loadings in mg. radium equivalent are shown at the top of each cartridge. The overall active lengths are also indicated.

cal position. The plastic collar is a friction fit on the outside of the tube and can be moved up and down to adapt to different lengths of uterine cavity. The collar is perforated so that it can, if desired, be sutured to the cervix. After the radioactive cartridge is introduced, the distal end of the tube is sealed by a solid vinyl rod, which is dipped in solvent (cyclohexanone), and slipped into the end of the tube. The rod welds firmly and rapidly to make an extremely strong watertight joint. When the source is to be removed the tubing is cut with scissors. Should it be necessary to change the source during a period of treatment, the tubing is severed, the source removed, and the replacement source is then retained by means of a small vinyl cap sealed onto the cut end of the tube with the same solvent.

The vaginal portion of the applicator consists of a pair of short cylinders separated by two removable stainless steel springs. A vinyl tube leads from the center of each cylinder to the outside. When the source cartridge is introduced, the actual source (dimensions of active volume = 6 mm.×2 mm.) locates at the geometric center of the cylinder. Lead disks (5 mm. total thickness—approximately 1 half value layer for Cs^{137}) are built into some of the cylinders on both the anterior and posterior aspects of the source. Other cylinders are made with lead at one end only and others are made without lead. The choice of cylinders for any particular case depends on whether it is designed to protect the rectum or bladder (or both or neither). In practice, a choice is made between the three differently shielded types of vaginal applicators and the appropriate sterile package is selected. Where there is insufficient space to take advantage of the springs (for separation of the cylinders) these can be discarded. Should there still be insufficient space at the vaginal vault, the cylinders can be pared down to size with a scalpel (Fig. 15). The cylinders (including lead disks), springs and uterine tube are all considered disposable. Figure 16 shows diagrammatically the loaded applicator in position in a patient.

DOSIMETRY

There has been little or no experience to date with the interstitial or intracavitary use of Cs^{137}, although other gamma ray emitting isotopes such as Co^{60}, Ir^{192}, Au^{198} and Ta^{182} have been used for these purposes for many years. There is, on the other hand, considerable experience with the use of Cs^{137} as a teletherapy source.[4,6,11,21,28,34,49] Although their gamma ray energies differ from one another, the isotopes mentioned above are not considered to have any significant biologic difference (RBE), and dosimetry schemes for them have been freely adapted from the standard concepts of radium dosimetry. It would seem reasonable, therefore, to make similar "concessions" for Cs^{137} since its gamma ray energy falls somewhere in the middle of the energy range for this whole group of isotopes.

From a clinical point of view the scope of intracavitary therapy is the treatment of the primary lesion and its immediate extensions. There is, in fact, some evidence to suggest that for Stage I and Stage II cases, this treatment alone may be sufficient.[39] On the other hand, once the disease has extended far out into the pelvis to approach or reach the lateral pelvic wall, intracavitary therapy will not provide adequate dose to the whole tumor. The emphasis then shifts to external therapy and intracavitary treatment becomes supplementary.[12,50] With modern supervoltage equipment or with Co^{60} teletherapy, adequate dosage can easily be delivered throughout the entire pelvis and thus compensate for any defi-

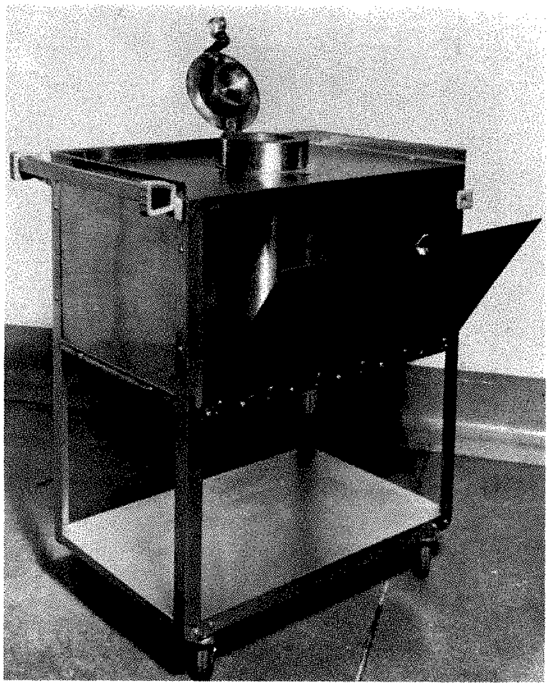

FIG. 13. The mobile cesium 137 lead safe is simple and rugged in construction. Long vertical holes which accommodate the cartridges are beveled at the top to allow for easy insertion and withdrawal with forceps. Each bevel is color coded to correspond with the cartridge it accommodates. The code, with full information about active length, strength of cartridges, etc., together with a decay chart for Cs^{137}, are kept in or on the cart. The unit as shown weighs about 150 pounds.

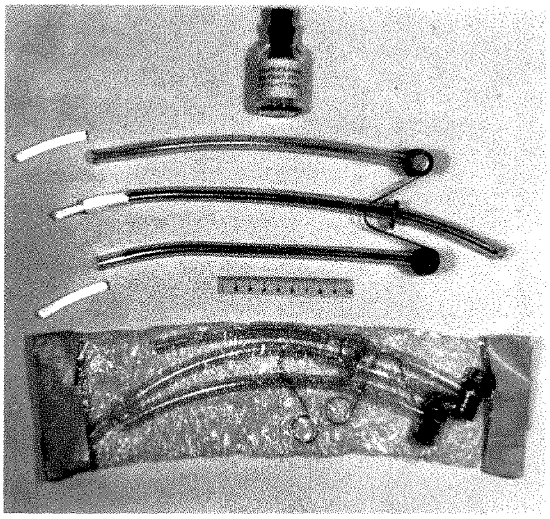

FIG. 14. The complete assembled disposable applicator is shown containing source cartridges in 2 of the 3 tubes. Each tube is sealed by dipping the small solid plastic rods in cyclohexanone (in the bottle), and by slipping them into the ends of the tubes. Welding occurs rapidly and firmly. At the bottom of the photograph, a complete applicator is shown in a plastic bag, sterile and ready for use. The springs, of course, are discarded if there is insufficient space at the vaginal vault to warrant their use.

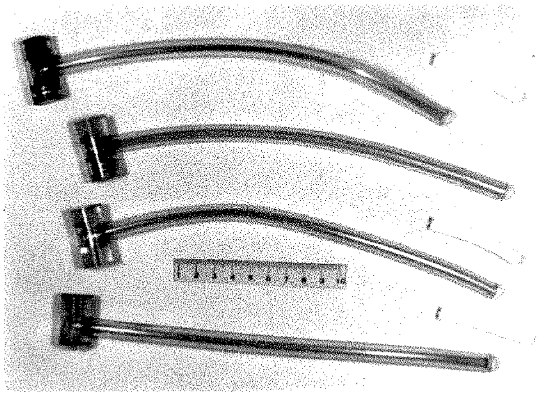

FIG. 15. There is a choice of 3 different types of vaginal cylinders for the colpostat. From above down in the photograph they are: (1) with 5 mm. lead on either side of the source for rectal *and* bladder protection; (2) with 5 mm. lead on one side of the source for protection of the bladder *or* rectum; and (3) with no built-in lead. At the bottom of the photograph, an applicator has been pared down on one side (by means of a scalpel) to illustrate that this equipment can be fitted where there is diminished space in the upper vagina.

ciencies laterally in dose level from the intracavitary sources. The importance, therefore, of a small difference between cesium 137 and radium dose at the lateral pelvic wall is minimized or eliminated.

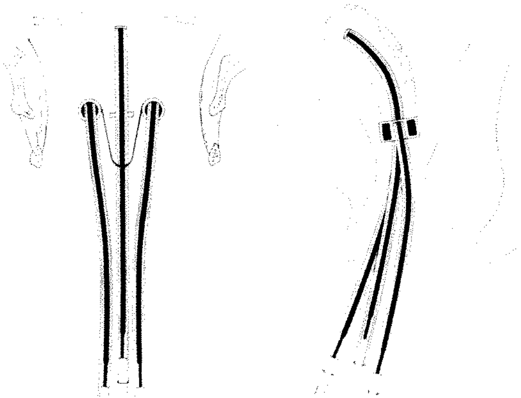

FIG. 16. Diagrammatic representation of the loaded applicator *in situ* within a patient. The solid black rods represent the source cartridges. The positions of the actual sources have not been indicated; however, the solitary vaginal sources are at the geometric centers of the cylinders and the active length of the intrauterine source corresponds to the distance from the external os to the uterine fundus. In the lateral view, protective lead disks are shown both anterior and posterior to the vaginal sources.

Because in the Cs^{137} treatment system described, the basic disposition of the sources within the pelvis is orthodox, dosimetric considerations will be similarly orthodox. The vaginal sources have a small active volume (6 mm. long cylinder × 2 mm. diameter) compared with standard radium tubes, but this will not significantly affect dose distribution within the pelvis. Theoretic calculations have been made to estimate the magnitude of the dosimetric difference between Cs^{137} and radium in tissue. In equilibrium with its daughter products radium has a complex spectrum of high and low energy gamma rays; however, the weighted mean average of the energy is somewhere in the region of 0.8 mev. (Table II). If this is compared with the monoenergetic 0.66 mev. emission of Cs^{137}, the following calculations can be made:

$I_{Ra}(x)$ = radium intensity at distance x cm.

$I_{Cs}(x)$ = cesium 137 intensity at distance x cm.

(assuming equal curiage of each)

TABLE II

PRINCIPAL GAMMA LINES FOR RADIUM AND ITS DECAY PRODUCTS SHOWING RELATIVE PERCENTAGE OF EACH ENERGY EMITTED

Energy (mev.)	% Weight
0.18	0.5240
0.241	5.0218
0.294	11.2664
0.350	19.6506
0.607	28.7336
0.766	2.8384
0.933	2.9258
1.120	8.9956
1.238	2.7511
1.379	2.7948
1.761	11.2664
2.198	3.2314
Total	100.0000

$\bar{E}$ = 0.781 mev. (weighted average radium γ energy).

(Adapted from JOHNS, H. E. The Physics of Radiology. Charles C Thomas, Publisher, Springfield, Ill. Second edition, 1961, p. 469.)

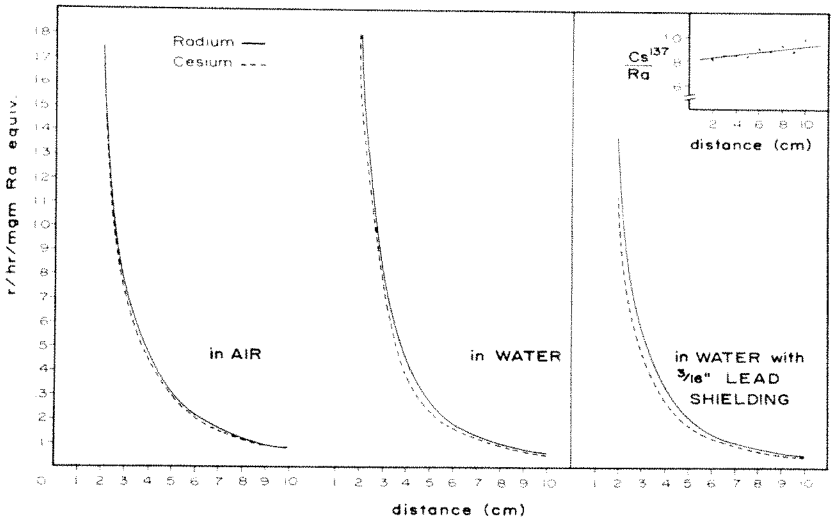

Fig. 17. Measurements for "equivalent" radium and cesium 137 sources are compared. Although the sources were identical in activity, their actual dimensions and construction differ and this accounts for some of the differences seen in the readings. Measurements in air at various distances from the sources show negligible differences. Measurements in water show that the dose rates from cesium 137 (under the conditions of measurement) are slightly less than those from radium. It can be seen that in water the 3/16 inch lead shield gives about 20 per cent better protection for cesium 137 than for radium at distances close to the shield. At greater distances there is less difference in the degree of protection afforded, mainly because of scatter. At the top right the ratio of dose rates behind the lead shield for cesium 137 and for radium is shown for various distances up to 10 cm.

$$I_{\text{Ra}}(x) \propto \frac{e^{-\lambda_{\text{Ra}}x}}{x^2}$$

$$I_{\text{Cs}}(x) \propto \frac{e^{-\lambda_{\text{Cs}}x}}{x^2},$$

where λ_{Ra} and λ_{Cs} = linear coefficients of absorption for radium and cesium 137 respectively in water.

Expressing this as a ratio:

$$\frac{I_{\text{Ra}}}{I_{\text{Cs}}}(x) = e^{(\lambda_{\text{Cs}}-\lambda_{\text{Ra}})x}$$

Taking the following values[27] for λ_{Cs} and λ_{Ra}

$\lambda_{\text{Cs}} = 0.073$ cm.$^{-1}$

$\lambda_{\text{Ra}} = 0.0711$ cm.$^{-1}$,

the equation may be solved for x as follows:

when $x = 5$ cm., $\frac{I_{\text{Ra}}}{I_{\text{Cs}}}(5) = e^{.0095} \simeq 1.01$,

when $x = 8$ cm., $\frac{I_{\text{Ra}}}{I_{\text{Cs}}}(8) = e^{.0152} \simeq 1.04$.

Thus it can be seen that for comparable point sources of radium and cesium 137 at 5 cm. distance in a tissue equivalent medium radium gives about 1 per cent greater dose. At 8 cm. this difference is somewhat larger (4 per cent). By a similar approach, Jones[29] using data of Goldstein and Wilkins[16] calculates that the difference at 8 cm. is 5 per cent. Jones and Stacey[30] using highly refined instrumentation made measurements of dose distribution in water around radium and cesium 137 tubes of similar construction and external dimensions, and found that in the equatorial plane doses were identical (within the limits of experimental error) at distances of up to 8 cm.

Our own measurements differ only slightly from those of Jones and Stacey,[30] possibly due to the different instrumentation. Our equipment consisted of an anthracene crystal (3 mm. diameter × 3 mm. long)

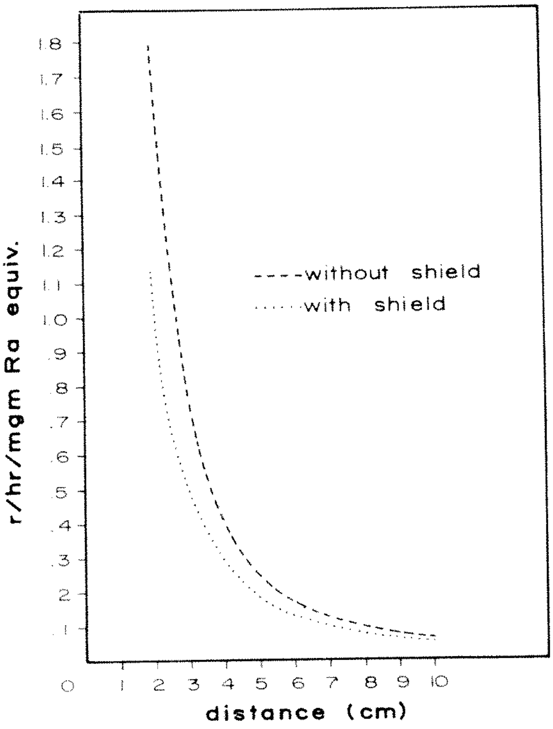

Fig. 18. Cesium 137 measurements in water illustrating the effect of a lead disk (3/16 inch thick and 1 cm. diameter) at various distances up to 10 cm. It can be seen that in clinical use such a shield can afford considerable dose reduction to the rectum or bladder.

located at the end of a stainless steel tube and attached via a lucite light pipe to a side window photomultiplier tube. Measurements were made in a tank of water and dose rates were recorded with a rate meter. Minor sources of error in a system such as this include energy dependence of the crystal, some filtration of the low energy scattered photons by the stainless steel tube and some slight response of the light pipe to irradiation.

The results of our measurements are presented in Figures 17 and 18. A solitary source was supported in the center of the tank and measurements were made at various distances for radium and cesium 137. Additional measurements were also made using a lead shield, 3/16 inch thick and 1 cm. in diameter, held a few millimeters from the source. Initially, a series of measurements were taken of dose rates from comparable radium and Cs^{137} sources at various distances in air and water. Although these sources were comparable in strength, they were not identical in their construction and their active lengths differed slightly. The ratio of Cs^{137} dose to radium dose can be seen to be unity in air at distances of up to 8 cm. In water, however, there is a somewhat greater attenuation of the Cs^{137} radiation, but this only amounts to a few per cent and is probably insignificant from a clinical point of view (Fig. 17). The extent to which the 5 mm. lead shield is effective for Cs^{137} in water is shown in Figure 18.

By drawing isodose lines around Cs^{137} sources of known radium equivalency (data taken from measured values) composite isodose curves can be constructed showing the radiation distribution in the coronal plane around an idealized implant. Such a distribution is shown in Figure 19 and

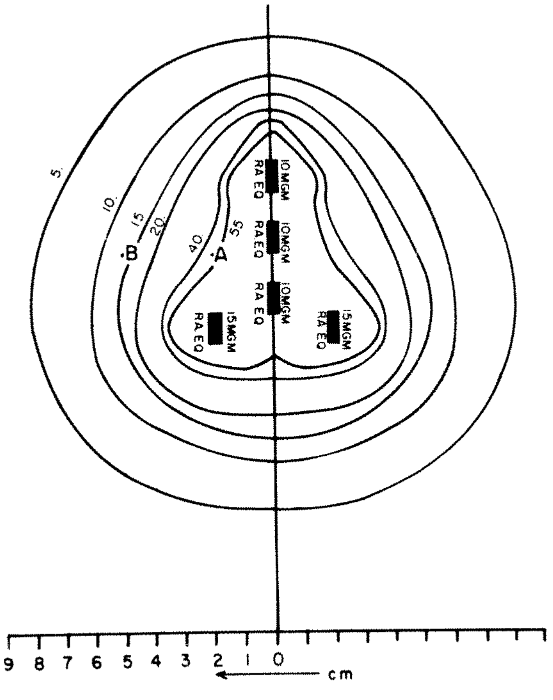

Fig. 19. Cesium 137 isodose lines in water phantom with the Paris type loading. The figures are in r / hr. This is an idealized situation and all sources and isodose lines are in one plane. It can be seen that with this source arrangement for 7,000 r at Point A, the Point B dose would be about 1,900 r.

Points A and B have been indicated to show the magnitude of dose fall-off from the paracervical region to the region of the lateral pelvic wall. Good separation of the vaginal sources has been allowed in constructing these curves.

SUMMARY

A complete system is presented for the intracavitary treatment of carcinoma of the cervix using cesium 137 instead of radium and incorporating several novel features.

The system uses an after-loading device which is disposable, and which can incorporate effective lead shielding for the rectum and/or bladder. The only permanent equipment is a small mobile lead safe containing sealed source cartridges, and thus the armamentarium required for carrying out the treatment is minimal and relatively inexpensive. Moreover, special facilities such as a Radium Room with all its associated equipment are not needed. Sterile packages of disposable plastic applicators can be purchased as required. The method is thus quite suitable for use in smaller hospitals where perhaps the case load is not great, and space and money are limited.

Some aspects of Cs^{137} for intracavitary use are discussed and some preliminary data and calculations on Cs^{137} dosimetry are presented.

The principal virtues of the system described are that it is inexpensive, easy and flexible in use, and that it reduces to an unprecedented minimum both *work* and *radiation exposure* for therapist, technicians and nurses.

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AN ANOMALOUS LYMPHOCYTE: POSSIBLY DIAGNOSTIC FOR EXPOSURE TO IONIZING RADIATIONS OR RADIOMIMETIC AGENTS*

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IN A previous study,[39] it was shown that bi- and trinucleated lymphocytes may be seen in the peripheral blood of normal, unirradiated mice and are not appreciably altered in their incidence following whole body x-irradiation even to 300 r. It was also shown that while relatively large cytoplasmic inclusions (nuclear satellites or fragments) in the lymphocytes of these mice were never seen in (13,000 lymphocytes of) normal, unirradiated mice, they did appear after whole body x-irradiation and continued to appear in the peripheral blood for 8 weeks in from 0.2 to 1.5 per cent of the leukocytes. The incidence of these cytoplasmic inclusions was not high. They have never been known to appear in the normal blood of any vertebrate. They have been reported in the early hematologic literature by Schwarz[42] in 1888. More recently, authors have described cytoplasmic inclusions in the blood of a few human cases of accidental x-irradiation exposure.[13,23,38,44,45] They are considered as anomalous lymphocytes,[40] and may be similar to x-irradiation caused nuclear debris.[2] Their presence may be useful as a diagnostic accessory to determine that whole body x-irradiation has been incurred. A study was planned to determine the incidence of these nuclear satellites or inclusion bodies following various increments of controlled whole body x-irradiation. The mouse is an ideal form for such a study since it normally has a high lymphocyte count, and the major part of this report concerns the results of this study.

MATERIALS AND METHOD

The mice were mature CF1 Swiss white strain which has been used in this laboratory for many years. Females alone were used in the earlier part of the study since they are known to be more radioresistant than the males, and in order to eliminate the sex variable. However, other CF1 mice of both sexes were studied and some were placed at 10° C. in total darkness for a period of 2 months in order to provide an unnatural stress factor which might induce anomalous conditions in the blood.[8]

Pregnant rats, both controls and x-irradiated (for another project) contributed blood for this study. Monkey fetuses were available, as well as newborn and adult monkeys, some of which were unirradiated controls and others had been exposed to x rays from 4 days to 2 weeks previous to the blood sampling. In addition, a variety of human fetal and adult material was made available. A single human fetus of 3 months of age had been subjected through its mother to 24 mg. of the radiomimetic nitrogen mustard. Patients with malignant diseases (such as Hodgkin's disease or lymphocytic lymphosarcoma or leukemia) and who were being subjected to chemotherapy and/or to x-irradiation were available for peripheral blood studies.

Complete blood cell counts were often made but this report will deal specifically with the lymphocytes. Percentage values are given in terms of total lymphocytes. Blood from the mouse or rat was taken from the tip of the tail or from behind the

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* From the Radiological Research Laboratory, Department of Radiology, College of Physicians & Surgeons, Columbia University, New York, New York.

Based upon work performed under Contract At-(30-1)-2740 for the Atomic Energy Commission and aided by Grant RH-81 from the Division of Radiological Health, Bur. State Service, Public Health Service. In this study the author has had the fine technical and photographic assistance of Csilla Makay, and also the efficient help of Jane Mower and Dolly Houston of the Hematology Department.

eyeball by means of a capillary pipette. From the monkey and human fetuses it was taken directly from the umbilical cord, and from the adult monkeys and humans from a finger. Smears were made in the usual way, air dried, and stained with Wright's stain.

Since the earlier study[39] had revealed a high incidence of these anomalous lymphocytes at about 2 weeks after whole body x-irradiation, the initial study was made at this postirradiation time but at exposure levels of 100 r to 500 r (at 100 r increments). Twenty-five females were used for each level of exposure and for controls. With this large number of animals, the severe lymphopenia following 500 r reduced the available lymphocytes for study to 1,715. The second phase of this study dealt with the daily fluctuations in the incidence of these anomalous cells, following 200 r and 400 r whole body x-irradiation. This study continued for 10 weeks. It then became necessary to determine the minimum whole body exposure which would elicit a single lymphocyte with a nuclear satellite, so exposures were graded from 100 r down to 10 r. Finally, 5 females were given 500 r whole body exposure and examined at hourly intervals until the first inclusion bodies in lymphocytes appeared.

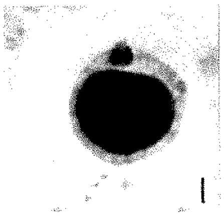
The x-irradiation was delivered at one time to the experimental animals, in various doses as indicated, but at a rate of 50 r/min. The physical properties were: parallel tubes with cross fire at 72 cm. distance from each tube to the center of the body of the mouse; filtration 0.28 mm. Cu, and 0.50 mm. Al; 184 kvp.; 30 ma.; and a half value layer of 0.6 mm. Cu.

EXPERIMENTAL DATA

The number of bi- and trinucleated lymphocytes among the control (nonirradiated) mice varied somewhat from about 2.2 per cent to 3.7 per cent of all lymphocytes, but they were present in every blood smear of normal and x-irradiated animals. The percentage in the lymph node smears was very low, as compared with the peripheral blood. Their numbers in the peripheral blood of x-irradiated mice were not significantly increased over the controls. No satellites have ever been found in the lymphocytes of unirradiated (control) mice of which, in the previous study, some 13,000 and in this study a total of 9,208 were examined. This aggregate of 22,208 control lymphocytes without any satellites should be convincing.

Table I shows that with increasing levels of whole body x-ray exposure the lymphocyte nuclear satellites appeared more frequently. The sole exception occurred after 500 r, where they appeared more frequently in the lymphocytes of the lymph nodes than in those of the peripheral blood. The lowest level of whole body x-irradiation of mice which produced any lymphocytes with these inclusion bodies was found to be 10 r.

From daily blood sampling of mice exposed to 200 r and 400 r, it was seen that these nuclear satellites appeared at the first postirradiation examination at 24 hours after exposure but then not again until the fifth day. This apparent interruption in their appearance may be related to the severe and almost immediate lymphopenia which follows acute whole body exposure coupled with their low incidence. The earliest appearance of nuclear satellites in peripheral blood was found to be 12 hours after exposure. Prior to this (at 7 hours after exposure), clusters of cytoplasmic granules, similar in staining properties to the larger satellites and the nucleus, were found in some lymphocytes (Fig. 10). These may be early manifestations of karyorrexis. The peak incidence (1.5 per cent) occurred at 13 days postirradiation following 400 r exposure. Since there were daily fluctuations in the incidence of these anomalous lymphocytes, the data are presented as weekly averages of 15 mice in Table II. Among the 3,538 lymphocytes of the unirradiated controls, no nuclear satellites were found, but in every instance and at any specific postirradiation weekly period, the average incidence was considerably higher for the satellites of animals exposed to the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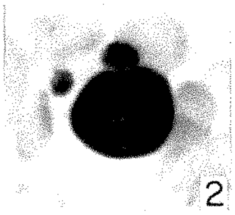
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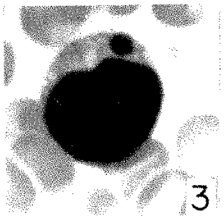
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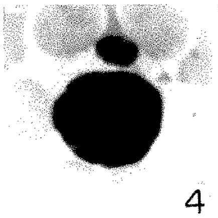
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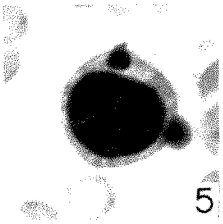
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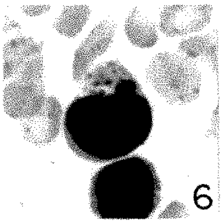
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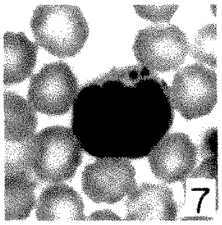
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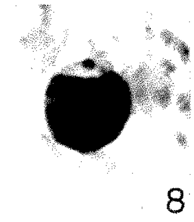
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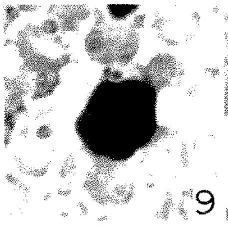
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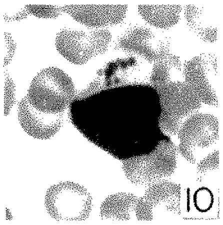
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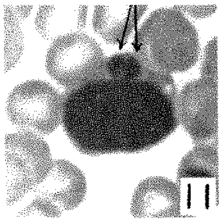
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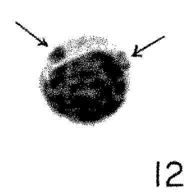
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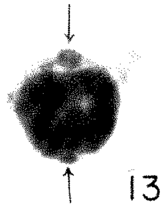
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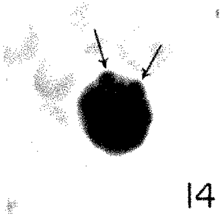
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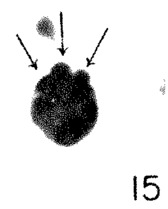
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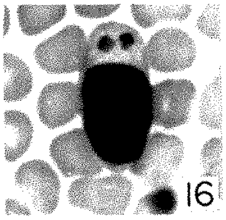
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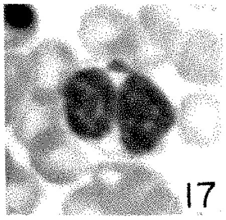
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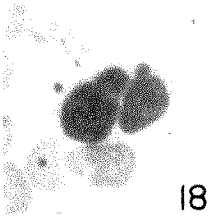
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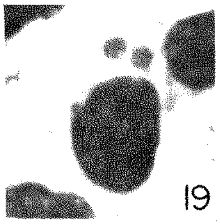
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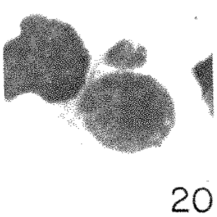
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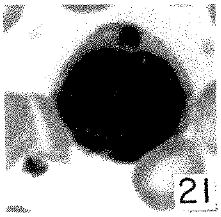
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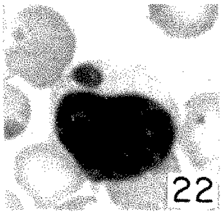
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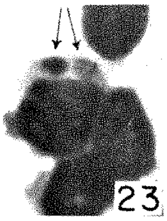
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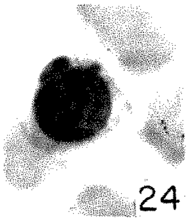
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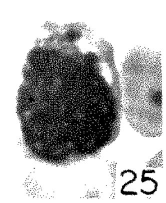
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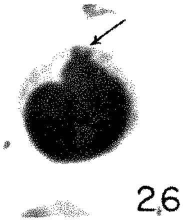
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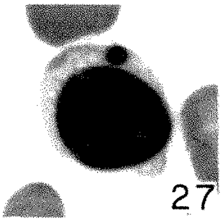
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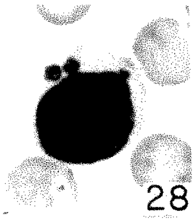
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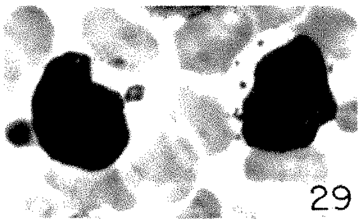
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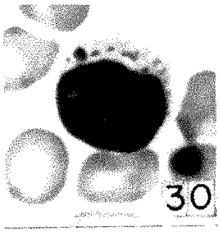
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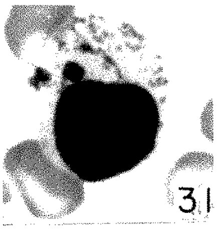
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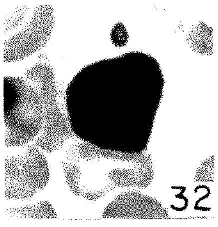
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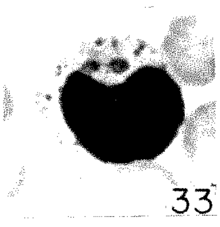
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higher level of irradiation (400 r over 200 r). Further, with each succeeding week the incidence increased to a peak at the fourth week, followed by a gradual decline to 10 weeks postirradiation, suggesting again that the damage must be to the precursors of the formed lymphocytes.

There were wide fluctuations in the incidence of the multinucleated lymphocytes, with the peak incidence at about 10–12 days and again at 6 weeks. The data in Table II show that there is no consistent change in the percentage of these cells with increasing levels of exposure, and their incidence fell below that of the controls during the first, fourth and ninth week. With respect to the nuclear satellites, the situation is quite different. It must be emphasized that on certain days the lymphopenia was so severe that it was difficult to find 200 lymphocytes from four smears of a single mouse, and when one is dealing with incidence of these satellites in the range of 0.12 per cent and upwards, it is really necessary to locate many cells. For this reason, each set of data is taken from a minimum of 1,247 lymphocytes.

It has not been determined whether other forms of stress might produce these anomalous lymphocytes. In examining mice which had been born and brought up for 3 months in a 10° C. temperature in total darkness, no nuclear satellites were found.

Blood of forms other than mice was available for these analyses. Pregnant rats, involved in another study, showed nuclear satellites in their lymphocytes only after whole body x-irradiation. Percentages were

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Plate I

Fig. 1–5. Large inclusion bodies in lymphocytes of CF1 mice following whole body x-irradiation to 200 r or more, seen from 24 hours to 8 weeks.

Fig. 6 and 7. Inclusion bodies in mice peripheral lymphocytes 24 hours after 25 r whole body exposure.

Fig. 8 and 9. Inclusion bodies in mouse lymphocytes found after only 10 r whole body exposure.

Fig. 10. Nuclear fragments found in the cytoplasm of a lymphocyte of mouse peripheral blood 7 hours after 500 r whole body exposure.

Fig. 11–13. Lymphocytes with double inclusion bodies in various positions within the cytoplasm in the mouse after x-irradiation.

Fig. 14 and 15. Lymphocytes in which 2 (Fig. 14) and 3 (Fig. 15) protrusions from the nucleus may be seen, suggesting possible origin of the inclusion bodies.

Fig. 16. Large and distinct paired inclusion bodies in mouse lymphocyte following x-irradiation.

Fig. 17 and 18. Binucleated lymphocytes each with an inclusion body, after x-irradiation of mice.

Fig. 19 and 20. Inclusion bodies in lymphocytes found in lymph node smears of x-irradiated mouse.

Fig. 21 and 22. Inclusion bodies in lymphocytes of peripheral blood from monkey fetus x-irradiated to 400 r and delivered 1 week later, and blood sample taken when 1 week of age or 2 weeks after x-irradiation.

Fig. 23. Double inclusion body in lymph node lymphocyte from monkey x-irradiated as fetus 1 week before delivery. Same as in Figure 21 and 22.

Fig. 24 and 25. Inclusion bodies in umbilical blood from human fetus at therapeutic abortion of patient treated only with nitrogen mustard (24 mg.) $2\frac{1}{2}$ months previously. No radiation therapy used (incidence 0.96 per cent).

Fig. 26 and 27. Lymphocytes from patient LY given a total dose of 1,500 r to mid-thorax showing formation of inclusion body (Fig. 26) and distinct body (Fig. 27) (incidence 0.55 per cent).

Fig. 28 and 29. Lymphocytes from patient G treated with chemotherapy and then with cobalt 60 radiation for lymphocytic lymphosarcoma (leukemia). This sample was taken after exposure to accumulated 750 r gamma rays in 5 days from Co^{60} (incidence 2.2 per cent).

Fig. 30–33. Patient S with small cell lymphosarcoma and no previous radiation therapy following 50 r betatron roentgen irradiation showing lymphocytes with inclusion bodies (incidence 0.63 per cent of all lymphocytes).

not determined. Monkey fetuses of both sexes, x-irradiated *in utero* in a neuropathologic study and sacrificed at various intervals after exposure, all showed the presence of these anomalous lymphocytes. The levels of exposure were 200 r or more directed to the fetus, and the time interval was at least 4 days. A fetal monkey exposed to 400 r *in utero* was delivered a week later and when it was 1 week of age (2 weeks postirradiation) blood sampling revealed lymphocytes with nuclear satellites (Fig. 21–23). Adult monkeys do not normally have these anomalous cells in their peripheral blood. Following x-irradiation of only the gravid uterus, they were occasionally seen in the monkey. A human (male) fetus, subject of a therapeutic abortion at 3 months, had been exposed when 3 weeks of age to nitrogen mustard (24 mg. nitrogen mustard, intravenously administered to the mother for Hodgkin's disease). This fetus showed nuclear satellites to the extent of 0.96 per cent of its lymphocytes (Fig. 24 and 25). A patient (L.Y.) given 1,500 r over the midthorax in 10 days in the treatment of metastatic carcinoma showed no double or triple nucleated lymphocytes but 0.55 per cent of such cells had nuclear satellites (Fig. 26 and 27). A patient (S) with small cell lymphosarcoma and no prior history of irradiation or chemotherapy showed no polynucleated lymphocytes prior to treatment, but there were 2 lymphocytes among 344 with short projections but no distinct cytoplasmic inclusions. Following 50 r betatron treatment, 0.63 per cent of his lymphocytes presented nuclear satellites and there was 1 double-nucleated lymphocyte among 789 cells (Fig. 30–33). Finally, another patient (G) had been given chlorambucil, 6 mg./day for 3 weeks and then 12 mg./day for 1

TABLE I

ABNORMAL LYMPHOCYTES FOUND 2 WEEKS AFTER X-IRRADIATION OF ADULT CF1 FEMALE MICE*

X-Ray Exposure	Total Lymphocytes	Binucleates (per cent)	Trinucleates (per cent)	Nuclear Satellites (per cent)
Controls				
Peripheral	4,350†	3.1	0.57	0.0
Lymph node	1,320	0.6	0.76	0.0
100 r				
Peripheral	6,000	4.3	0.01	0.15
Lymph node	406	0.7	2.46	0.0
200 r				
Peripheral	3,275	3.9	0.49	0.3
Lymph node	972	1.1	0.0	0.7
300 r				
Peripheral	2,875	4.0	0.66	0.76
Lymph node	820	2.0	0.0	1.30
400 r				
Peripheral	2,150	4.7	0.84	1.16
Lymph node	781	1.5	0.0	1.90
500 r				
Peripheral	1,715	5.8	9.93	0.27
Lymph node	159	0.6	0.0	3.10

* At least 25 female mice were x-irradiated at each dose level, and two smears made from each mouse. Due to x-irradiation lymphopenia, mice exposed to the higher doses yielded few lymphocytes to examine.

† Over 22,000 lymphocytes of normal, unirradiated CF1 mice have been examined without finding a single nuclear satellite such as referred to here.

week prior to cobalt 60 radiation therapy at 150 r/day. After receiving some 750 r in 5 days, he showed 2.2 per cent of 359 lymphocytes with nuclear satellites but no multinucleated lymphocytes (Fig. 28 and 29). The diagnosis of this malignancy was lymphocytic lymphosarcoma (leukemia). The hematologic literature describes such lymphocytic nuclear satellites only in abnormal cells[40] in Chediak's syndrome for acute leukemia of childhood in which some of the lymphocytes included, in their cytoplasm, nuclear satellites which were probably DNA[31] and, recently, in several nuclear accidents.[23,38]

DISCUSSION

The lymphocytes of the peripheral blood are believed to live 6 to 24 hours[5] and are recognized as probably the most radiovulnerable of all cells of the mammalian body with the exception of spermatogonia.[3] The relative decrease in lymphocytes (lymphopenia) can be equated with the degree of whole body exposure to ionizing radiations.[3,10,11,14,15,25,26,30,31,32,34,43,46] This sudden decrease in the formed lymphocytes of the peripheral blood appears to be related to possible mitotic radiosensitivity, but may also be related to direct destruction. Thus, one can expect an almost immediate decrease in the number of formed lymphocytes in the peripheral blood as a result of destruction of their precursors following the x-irradiation of any vertebrate.[37,49]

Some of the precursors of the mature lymphocytes, which survive whole body x-irradiation and are found in the hematopoietic organs, may exhibit cytoplasmic and nuclear changes such as pyknosis, karyorrhexis, intranuclear and cytoplasmic vacuolization, lobulation and possible fragmentation of the nucleus, and the appearance of cytoplasmic inclusions.[12,39,42,44,45] All of these cytologic effects have been described for other x-irradiated cells, but the lymphocyte and its precursor seem to be particularly vulnerable to ionizing radiations.

Table II

POSTIRRADIATION WEEKLY AVERAGE CHANGES IN ABNORMAL LYMPHOCYTES OF ADULT CFI FEMALE MICE*

Week	Dose	Total Lymphocytes	Binucleates (per cent)	Trinucleates (per cent)	Nuclear Satellites (per cent)
	Controls	3,538	2.2	0.26	0.0
1	200 r	2,550	1.4	0.20	0.12
	400 r	1,675	4.1	0.92	0.50
2	200 r	2,150	2.6	0.43	0.14
	400 r	1,265	4.0	0.61	0.92
3	200 r	2,707	2.5	0.52	0.25
	400 r	1,766	3.2	0.70	1.07
4	200 r	3,448	1.7	0.14	1.00
	400 r	3,192	1.5	0.16	1.20
5	200 r	1,954	0.45	0.05	0.35
	400 r	1,247	1.28	0.16	0.88
6	200 r	430	5.5	0.55	0.46
	400 r	371	2.4	0.27	0.81
7	200 r	557	3.0	0.38	0.54
	400 r	382	4.4	1.0	0.78
8	200 r	466	3.0	0.0	0.21
	400 r	539	1.1	0.37	1.1
9	200 r	859	0.94	0.21	0.0
	400 r	918	0.24	0.42	0.21
10	200 r	500	1.4	0.0	0.0
	400 r	533	2.7	0.36	0.18

* At each of the two dose levels, 15 female mice were examined daily over the 5 week period, samples of blood being taken from 2 mice each day with intervals of a week for the repeated sampling from the same mouse. Following this, analyses were made weekly. The above data are total counts at the end of each of 10 successive weeks.

It has long been suggested that bi- and trinucleated lymphocytes appear in persons exposed to small doses of ionizing radiations.[6,7,16,22,30,31,32,53] In fact, a very low level of exposure (12–15 r) is said to have caused the production of "these abnormal forms."[53] The lymphocytes of nonleukemic individuals show a quantitative response to only 2 r.[41] Such multinucleated lymphocytes appear normally in the peripheral blood of the unirradiated control CF1 Swiss mice up to 3 per cent of their leukocytes[39] and the incidence was not appreciably changed following whole body exposures up to 500 r during a continuing study for 12 weeks postirradiation. In this study 400 r did not elicit any correlating response in these cells during 10 weeks. It is doubtful that these polynucleated lymphocytes can have much radiation-diagnostic significance in CF1 mice, since they are always present, and their incidence is not affected by whole body x-irradiation.

The lymphocyte cytoplasmic inclusions (or nuclear satellites) here reported are not to be confused with the small and highly refractile cytoplasmic granules first described by Gall,[9] which bodies are said to occur commonly in 34 per cent of the unstained lymphocytes. Gall's granules were neutral red staining and have been variously described as particles, particulates, bodies, granules, or inclusions.[12] They have been seen frequently by others[4,13,27] and are described in the hematologic encyclopedia. The number of these particles in unstained lymphocytes does not seem to be increased in persons receiving large exposures of radioiodine.[51] They may be related to the phospholipid droplets in liver and other somatic cells, as described by Palade and Claude,[35,36] and Wallgren.[33,50] They are soluble in fat solvents, in cold alcohol, and in strong but not weak acid or base. They stain with lipid stains and basic dyes and are increased in number by the action of neutral red or supravital preparations of blood.[12] Gall's granules are therefore much smaller and chemically different from the nuclear satellites of this study. One cannot exclude the possibility that some occasional granules or bodies may be present by virtue of the demonstrated phagocytic activity of (human) lymphocytes,[29] even though it has been stated that from 7 to 13 days after exposure the leukocytes show a markedly reduced capacity to phagocytize bacilli.[1,52]

It is contended here that the cytoplasmic nuclear satellites described and illustrated in this study (Fig. 1–33), which have never been seen or described in the blood of unirradiated mice,[41] are not the previously described granules of Gall, but are, in fact, nuclear fragments which probably result from the direct karyorrhectic action of ionizing radiations on the nucleus of the radiosensitive and differentiating lymphoblasts. Such a suggestion has recently been supported[23,38] in a study of human peripheral blood following nuclear accidents. These cytoplasmic inclusions were described as nuclear fragments and were Feulgen positive. The man in the Lockport accident[23] had received 1,500 r to the head and shoulders and 300 r to the whole body, and the peak incidence of these satellites was 4 per 1,000 (0.4 per cent) lymphocytes 28 days after exposure.[24]

The fragmentation or pinching-off of parts of the nucleus may be comparable to the sloughing off by the embryo of radiation-necrotized cells which leave a deficit embryo. In the case of the lymphocyte or its precursor, the lymphoblast, there may be a discarding into the cytoplasm of that portion of the fragile nucleus which is radiation-damaged. It may be that this lymphocyte nucleus attains its maximum radiosensitivity during maturation process. The inclusion is usually larger than the so-called sex chromosome, and is found in lymphocytes of both sexes. It is believed that these cells are moribund and could not be cultivated. Since these cytoplasmic inclusion bodies are not found in the formed peripheral lymphocytes immediately after exposure, the fragmentation must occur in the pro-lymphocyte or lymphoblast stage, or during the maturation process. The immediate origin of lymphocytes is not yet established, but it may be conjectured that this fragmentation occurs in any of the precursor cells such as lymphoblasts, or even earlier in the reticulolymphocytes or even myeloblasts. This is based upon the fact that these cytoplasmic inclusion bodies first were seen here to appear at 12 hours after exposure and remained in the peripheral blood for about 10 weeks, depending upon the level of exposure. The pro-lymphocyte is insulted before it reaches the peripheral blood stream, probably while in one of the hematopoietic organs, and appears subsequently (7–12 hours) in the peripheral blood. Since it may be found for 10–12 weeks after irradiation, this period probably represents the period of maturation of some lymphocytes. Inclusion bodies were found in the differentiating lymphocytes of the lymph nodes of all x-irradiated animals examined. The texture and staining proclivities of these satellites are similar to those of the nucleus, with which they are often closely associated. This concept has a corollary in the studies with other sensitivities, wherein it has been shown that the formative or differentiating stage of any cell is the most radiosensitive, even more so than the subsequent completely differentiated stage. The persistence of these cytoplasmic inclusions (or nuclear fragments or satellites) up to 10 weeks after 400 r whole body exposure and their identification in the lymph node smears at least after 2 weeks strongly suggest that damage may be incurred while the formative cells are in the hematopoietic organs.

SUMMARY

1. The bi- and trinucleated condition was found regularly in control (unirradiated) CF1 female mice to the extent of 2 to 4 per cent of all lymphocytes. *Cytoplasmic inclusions*, which are believed to be fragments of the nucleus (nuclear satellites), were never seen in over 22,000 normal mouse lymphocytes examined. They have never been reported in normal human blood.

2. At 2 weeks after whole body exposure to x rays, there was no evidence of any significant increase in the multinucleated lymphocytes, even in exposures up to 500 r. The lymphocyte cytoplasmic inclusions (nuclear satellites) were found in the peripheral blood after all levels of exposure from 100 r to 500 r, in frequencies from 0.15 per cent to 1.16 per cent, and in higher incidence in lymphocytes in lymph nodes. There was a definite increment in the incidence of these inclusion bodies when exposure levels were increased.

3. In a daily study of the peripheral blood of x-irradiated mice (200 r and 400 r) for 10 weeks, it was found that the cytoplasmic nuclear satellites in lymphocytes were seen regularly beginning at 1 day. The peak incidence occurred between 2 and 4 weeks postirradiation, but they were also found as early as 12 hours and after only 10 r exposure.

4. The inclusion bodies appeared to be fragments of the nucleus (nuclear satellites), their structure and staining proclivities being the same. Karyorrhexis is a situation known to other somatic cells following high levels of x-irradiation and the lymphocytes have long been recognized as particularly radiosensitive.

5. The stress of continued low temperature (10° C.) for 3 months did not produce these inclusion bodies in lymphocytes in mice. While it is possible that other forms of stress might produce such bodies, ionizing radiations and radiomimetic agents (nitrogen mustard or chlorambucil) appear to be particularly effective in causing karyorrhexis.

6. Lymphocyte cytoplasmic inclusions, which seem to be nuclear fragments or satellites (karyorrhexis), appeared in the peripheral blood of mice, rats, fetal and adult monkeys, and in several humans with malignant diseases after treatment with a radiomimetic agent and/or x-irradiation. While the incidence of these anomalous cells was not high, the fact that they were never seen in normal mouse, rat or monkey blood and have never been described in *normal* human blood suggests that their presence may be an accessory fact in diagnosing a prior possible exposure to ionizing radiations.

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X-RAY SPECTROPHOTOMETRY IN VIVO*

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IN QUANTITATIVE analysis by spectrophotometry, the choice of wavelengths of the electromagnetic spectrum is determined by the optical properties of the material to be analyzed; infrared, visible and ultraviolet light are the bands most commonly used. Spectrophotometry by means of x-rays seems to have been described in detail for the first time in 1925 by Glocker and Frohnmayer.[3] It has since been developed as an extremely sensitive method for elementary analysis in microradiography.[1]

During the last 10 years, techniques have been worked out for the quantitative determination of certain elements and substances in the living body by means of absorption measurements using monochromatic x-rays. The present article is devoted to the principle involved, the experimental techniques and a summary of the results so far obtained.

PRINCIPLE

The transmission of x-rays by a substance depends upon its elementary composition and the wavelength distribution. In Figure 1 the transmission has been plotted as a function of the wavelength for certain amounts of soft tissues, bone salt (hydroxyapatite) and iodine. Since these curves are different in shape, it is possible to compute the amounts of these substances present in a mixture from the absorption values of three monochromatic wavelengths.

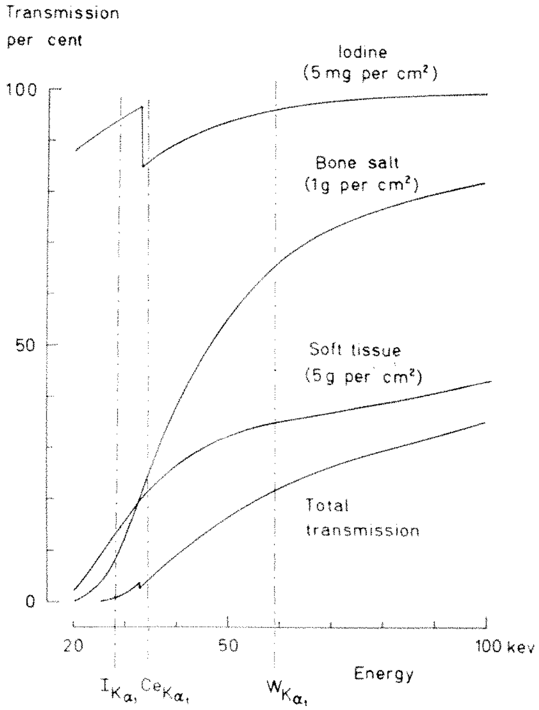

FIG. 1. Transmission plotted as a function of x-ray wavelength for various substances individually and combined.

In general, to analyze n elements or substances, absorption measurements at n wavelengths are required. This follows from the fact that the simultaneous equations obtained by the application of Lambert's law can be solved only if the number of equations (m) is equal to the number of elements (n);

$$
\begin{aligned}
I_1 &= I_{0,1} \exp\left[-(\mu_{1,1}x_1+\mu_{1,2}x_2+\cdots+\mu_{1,n}x_n)\right]\\
I_2 &= I_{0,2} \exp\left[-(\mu_{2,1}x_1+\mu_{2,2}x_2+\cdots+\mu_{2,n}x_n)\right]\\
&\vdots\\
I_m &= I_{0,m} \exp\left[-(\mu_{m,1}x_1+\mu_{m,2}x_2+\cdots+\mu_{m,n}x_n)\right]
\end{aligned}
\tag{1}
$$

where I and I_0 are the transmitted and incident intensities, respectively, μ the mass absorption coefficients, x the amounts

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The term dichromography has been used previously for the new technique; "X-ray Spectrophotometry" would seem to be a more appropriate designation, and will be used here.

of the elements present, expressed in grams per square centimeter, the subscripts 1 · · · m refer to the different wavelengths and the subscripts 1 · · · n to the different elements. In order to solve equations (1) it is furthermore required that the relationship between the wavelengths and the values of μ for the various substances should differ significantly for the respective substances.[3,7,8,9]

The choice of wavelengths is governed by several factors. If the continuous part of the mass absorption curves is employed, the following rules apply. The longest wavelength, corresponding to the highest absorption, should be chosen to give the highest permissible attenuation at the thickest part of the object. The attenuation is limited by the required number of transmitted quanta; for if it is too high, the number of quanta will be too small, and this will result in too large a statistical fluctuation in the transmitted beam for the desired accuracy of the determination. In principle, another factor that limits the permissible attenuation is the maximum radiation dose that can be given to the patient.

The shortest wavelength is usually chosen as remote from the longest wavelength as possible. In practice the difference is limited, as there is a tendency for the purity of the soft radiation from the x-ray tube to be impaired when the difference is made large. Moreover, there is a minimum number of high energy quanta consistent with statistical accuracy, which also limits the difference. The choice of the shortest wavelength thus involves a compromise between several factors.

When three elements or substances are analyzed using the continuous part of their mass absorption curves, the third wavelength is chosen between the two others so as to give the highest accuracy in the solution of equations (1). For any particular maximum thickness and composition of the object, the appropriate wavelength can be calculated numerically. This involves finding the most accurate solution of equations (1). As an approximation, the third wavelength corresponds to an energy that lies at a point situated one-third of the interval between the highest and lowest energies, reckoned from the low energy point. This method of analyzing three elements by means of their continuous absorption curves is at present, however, of mainly theoretical interest since the available sources of monochromatic radiation are too weak to permit a practical application. When the continuous mass absorption curves are employed, therefore, x-ray spectrophotometry *in vivo* is for the time being restricted to the analysis of only two substances.

The above comments on the choice of wavelength do not hold if any analyzed element of the object has an absorption edge at a wavelength shorter than the selected longest wavelength. The greatest sensitivity is then obtained if two wavelengths are chosen as close as possible to, and on the opposite sides of the edge.[3,9] In the example in Figure 1, the absorption edge for iodine is at 33 kev. (0.37 Å), and the preferred wavelengths are the K emission lines of iodine and cerium. The shortest third wavelength, when analyzing three substances, should still be as far as possible from the other two.

In the above discussion no clear distinction has been drawn between elements and other substances. The reason is that the elements composing the tissues of the living body are present in fairly constant proportions, so that it is practical to calculate effective mass absorption coefficients.[8] The coefficients for water and proteins differ by too small an amount for them to be discriminated, and they must therefore be determined together; they can, however, be distinguished from hydroxyapatite and fat. Iodine is analyzed as the pure element when its absorption edge at 33 kev. can be used. In general, elements with atomic numbers greater than that of iodine can be analyzed in bodies up to about 10 cm. thick by means of their absorption edges, whereas the energies at the edges for lighter elements

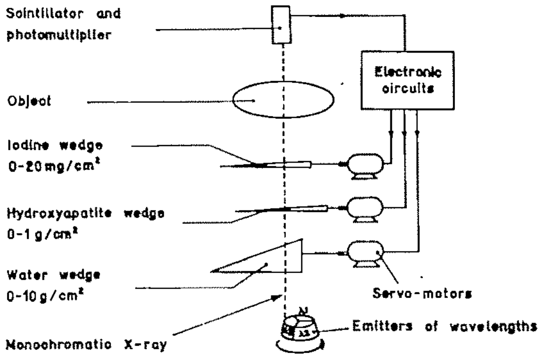

FIG. 2. Principle of the analog computer.

are so low that the attenuation becomes too large for accurate analysis.

TECHNIQUES

For x-ray spectrophotometry *in vivo* to be possible, two major experimental difficulties must be overcome. Firstly, monochromatic or, at least, homogeneous x-rays must be generated at high enough intensities; and secondly, accurate absorption measurements must be carried out during the limited time a living object can remain motionless.

Monochromatic x-rays can be produced by several methods, all of which, however, yield low intensities. It has therefore been necessary to develop methods for obtaining homogeneous radiation of higher orders of intensity than have previously been achieved. Two principles have been tested, namely, primary and secondary excitation.

The best results have been obtained hitherto by secondary, or fluorescent, excitation from a special x-ray tube.[6] The homogeneous radiation is obtained from a conical secondary target placed inside the primary target, which consists of a gold-plated copper foil cylinder. The short distance (0.1–0.3 cm.) between the primary and secondary targets results in a high yield of secondary radiation, of the order of 10^8–10^9 quanta per milliampere-second-steradian. The greatest advantage of tubes of this type is that the secondary targets may be made of a large range of heavy elements compounded with elements of low atomic number.

Fairly homogeneous radiation can be obtained from a conventional tube with primary excitation employing selected elements or substances as a target provided that the tube voltage is suitable and that the beam is properly filtered. This primary excitation method has the advantage over secondary excitation that slightly higher intensities can be obtained for the same input energy and size of tube; there are, however, few materials that are suitable as targets in a high vacuum tube.

To solve equations (1) it is necessary to determine the absorption of the monochromatic x-ray beams with great precision, since the analysis relies on the determination of differences in absorption values that are often nearly equal in magnitude. In fact, the absorption values must be accurate to at least 1 per cent, occasionally to within 0.1 per cent. The accuracy is needed also when, as is often the case, the total absorption varies with the thickness of the object traversed by the beam by a factor of 100 or more. This places stringent demands on the linearity of the method. In the determinations speed is also of paramount importance if, for instance, errors due to movement of the object are to be avoided.

The basic principle of an analog computer that fulfills the above requirements is shown in Figure 2. In this example, the three substances being determined are iodine, hydroxyapatite (bone salt) and soft tissues consisting of water, proteins and fat. Three monochromatic x-rays emitted in succession by the tube pass through three absorption wedges and the object to a scintillator detector. The wedges are composed of the substances being analyzed—in this case, iodine, hydroxyapatite and water. Water is assumed to have the same absorption as the soft tissues of the body. (The error incurred by making no distinction between fat and other soft tissues will be discussed below.) The position of the wedges is automatically adjusted by means of the electronic circuit to give constant

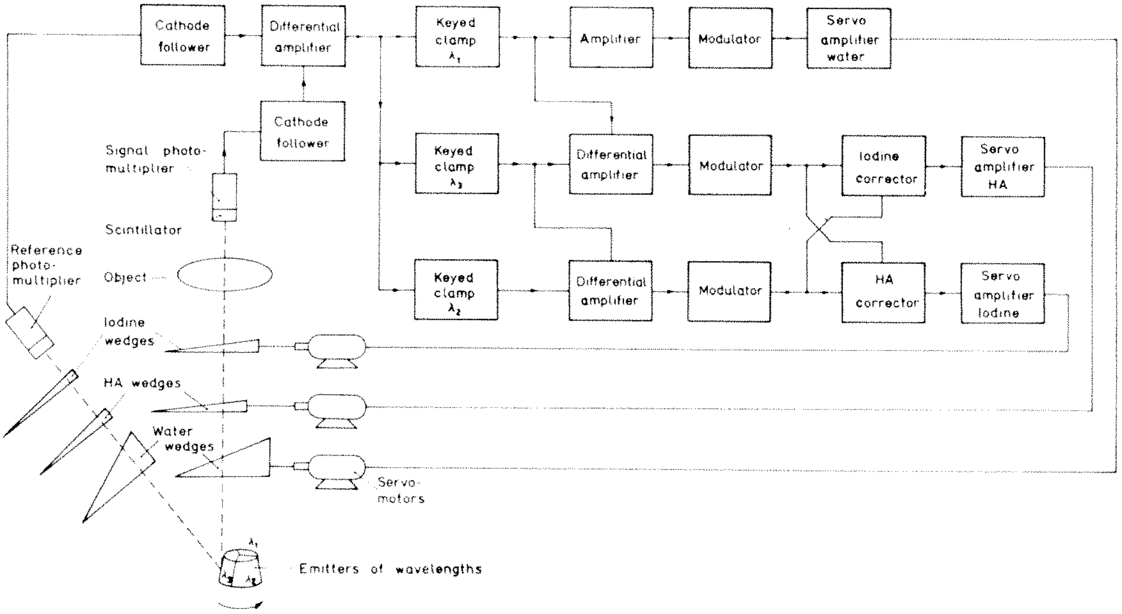

FIG. 3. Simplified block diagram of the analog computer.

intensities of the three wavelengths incident on the scintillator. Before the object is placed in the beam, the x-rays pass through the thickest part of the wedges. When the object is placed in the beam, the wedges are automatically withdrawn a certain distance, which corresponds to the amount of iodine, bone salt and soft tissues in the object. Thus, the displacements of the three wedges constitute a quantitative measure of the amounts of the substances in the traversed volume of the object. The displacements of the wedges are plotted by ink recorders.

This multiple wedge system has certain valuable properties. (1) Since the amounts of the three substances traversed by the beam, and hence the attenuation, are constant for all wavelengths, any nonhomogeneous radiation affects the results to a much smaller degree than if the total absorption and composition traversed by the beam varied during the determination. If this were the case, the intensity of the nonhomogeneous longer wavelengths, for instance, would incur an error at thin parts of the object where the absorption is low, but not at thick parts. (2) Since the detector always works at constant input intensities, any nonlinearity in the detector circuit is of minor importance, whereas with a noncompensatory measuring system, the detector would have to be linear within, say, 0.1 per cent over at least a 100 fold scale of intensity. (3) The radiation dose that the object receives is always automatically reduced to the theoretical minimum; the number of quanta leaving the object is always limited to that for which the statistical fluctuations of the beam remain just below the level required by the desired accuracy of the determinations.

A simplified block diagram of the analog computer is given in Figure 3. The method is rendered independent of fluctuations in the x-ray beam by employing the null principle. Two similar x-ray beams are used: one reference beam with stationary wedges and one measuring beam with servo-controlled wedges. The reference wedges are used to set the measurement ranges for the various substances under analysis. The outputs from the two photomultipliers are fed into a differential amplifier. The appropriate balance points for the three simultaneous null systems—for iodine, hydroxyapatite, and water—are indicated by zero outputs from the differential amplifier for the three wavelengths. To control the servo-motors the gating of the error signals into the appropriate channels of the analog network is synchronized with the switching of the wavelengths. A major experimental difficulty when working with more than two wedges simultaneously is to prevent hunting; any coupled oscillation of the wedges results in false balance points. One way of avoiding this is to introduce a mutual correction of the error signal in the iodine channel for the error in the hydroxyapatite channel, and vice versa (Fig. 3). A detailed description of the analog computer will be published elsewhere.

The equipment can be used for measuring the amounts of substances in a particular volume of an object. Density profiles of the substance may be obtained by unidirectional scanning of the object with the measuring beam. By scanning in two perpendicular directions, stereograms can be obtained showing the quantitative distribution within a scanned volume of the object. The equipment is shown in Figure 4.

To explore the possibility of performing simultaneous determinations of four substances by means of four wavelengths, a fourth wedge containing fat was included. It was found, however, that because of the small difference in absorption between fat and other substances, only three wedges could be used simultaneously. Since four-wedge operation was impracticable, the description is limited to the three-wedge system; the iodine—hydroxyapatite—water combination has proved particularly useful. The most commonly employed wavelengths are given in Figure 1.

ERRORS

The main factor that limits the attainable accuracy in x-ray spectrophotometry is the statistical fluctuation in the quanta transmitted by the object. The accuracy is governed by the number of transmitted quanta according to statistical theory. Thus, in a two wedge system the number of quanta n required for nulling a wedge with a 95 per cent reliability is

$$n = 8/E^2$$

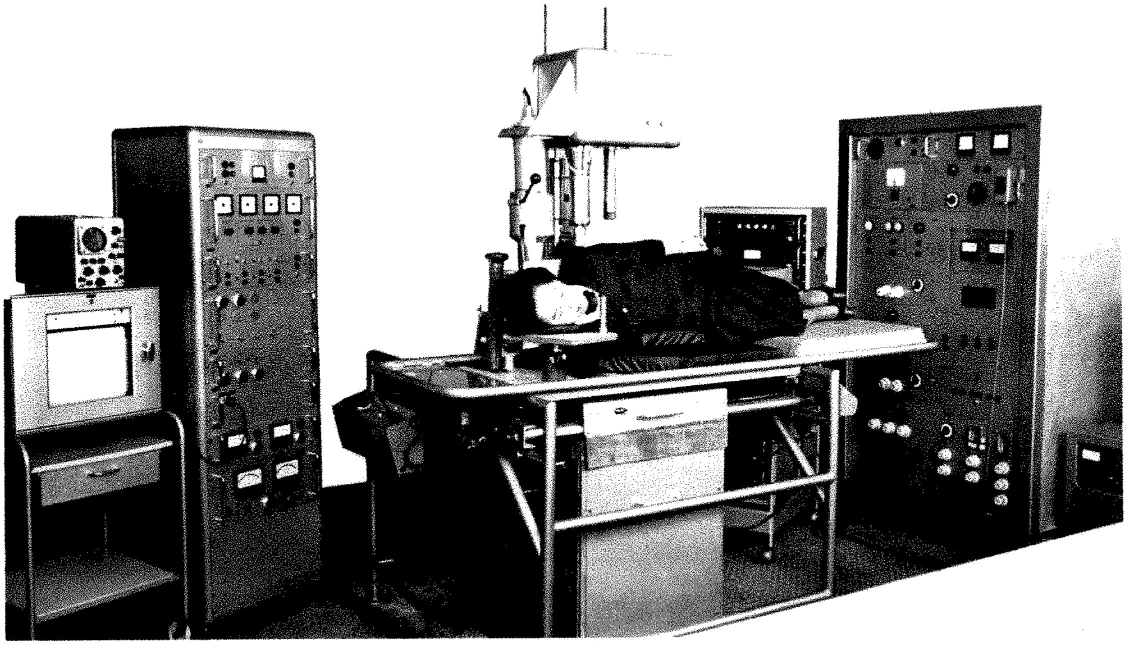

Fig. 4. X-ray spectrophotometer.

where E is the largest permissible error—expressed as fraction of the absorption—in the absorption difference at the two wavelengths. The error E, which is determined by the desired accuracy of analysis, may be calculated from the mass absorption coefficients and amounts of the substances present in the object. If the error E should not exceed 1 per cent, 80,000 quanta must be transmitted by the object. Then, 95 per cent of the absorption values are correct to the specified degree of accuracy.

If greater accuracy is desired n must be increased. This can be done by increasing either the number of incident quanta or the area of the x-ray beam scanning the object. The number of incident quanta can be increased either by raising the output of the x-ray tube, or, if this is not possible, by prolonging the measurement period for each volume of the object. Since for each monochromatic wavelength the absorption increases exponentially with thickness, a third important possibility may exist, namely compression of the object.

Related to these considerations is the speed of movement and the time required to balance the wedges. The speed of each wedge should be chosen to suit the statistical accuracy of the governing absorption measurement. In general, with present-day techniques, the speed is moderate, and the movement of a wedge over its full length covers 0.5 to 5 seconds. Thus, in the three-wedge system described above, when analyzing objects with a maximum thickness of 10 cm. and a beam cross-section of 0.2 to 0.7 sq. cm., the water wedge moves through its full length in 0.5 seconds and the hydroxyapatite and iodine wedges both in 2 seconds. With two wedges operating (the water wedge and either the hydroxyapatite or the iodine wedge), the balancing time then does not exceed 2.5 seconds, while with three wedges it is at least 20 seconds. The reason for the considerably greater balancing time with all three wedges is that the absorption differences must be determined with greater accuracy for a simultaneous estimation of the three substances to be possible. Moreover, the servo systems must be heavily damped to prevent coupled oscillations.

Systematic errors are incurred because of the approximations to uniformity of composition of the tissues in the object. These errors are of relatively minor importance, since the elementary composition of fat, protein and bone does not vary appreciably within a particular biologic species. A more serious problem is presented by the systematic errors that arise when any one of the substances, bone salt, fat or other soft tissues is neglected in the estimation of the two others or of iodine. Thus, when employing CeK_α and BaK_α radiation in iodine analysis by means of an iodine and a water wedge, 1.0 g. of fat is equivalent to 0.5 mg. of iodine, while 1.0 g. hydroxyapatite corresponds to -7.2 mg. of iodine. For this reason a hydroxyapatite wedge is essential in iodine analysis to prevent systematic errors. Similarly, in bone salt determinations, fat gives rise to a systematic error. For instance, in a two-wedge system with water and hydroxyapatite employing WK_α and CeK_α radiation, 1.0 g. fat gives rise to an error of -0.05 g. of hydroxyapatite.

Another systematic error arises when a strongly absorbant substance is unevenly distributed across the x-ray beam. If one sector of the beam is attenuated more than the rest, the amount of the estimated substance in the path of the highly attenuated sector will not be compensated for by a wedge displacement. Thus, it is essential that the object in the x-ray beam should be of sufficiently uniform thickness and composition and that the x-rays should not be too soft.

Scattered x-rays from the object might introduce an error if the scintillator is placed close to the object. Any such error could be eliminated by increasing the distance between the object and the scintillator, which involves no disadvantage.

Wedges can usually be moulded with sufficient accuracy for any error due to imperfection to be negligible. The quality of the wedges can be checked in the equipment by observing the wedge displacements caused by placing known samples of the substance in the beam.

DOSE

With the method described the radiation dose is kept close to the theoretical minimum. This is possible because (1) the x-ray beams are attenuated by the wedges to exactly the number of incident quanta needed to give the desired level of accuracy; (2) the object is exposed only to the wavelengths used for the analysis; and (3) all the information available in the emergent beam is utilized, all the quanta being trapped in the scintillator and processed in the analog computer. The method differs therefore from the other roentgenographic procedures, in which a broad x-ray spectrum is used of which only the incident quanta of high energy contribute significantly to the image; weakly absorbing regions are then often exposed to excessive radiation to enable the heavily absorbing regions to be examined; and in some systems a large fraction of the transmitted quanta pass through the recording medium owing to inefficient absorption.

The dose to which the patient is exposed is dependent upon the accuracy required of the determinations, the choice of wavelengths, the thickness of the object and the number of elements analyzed. The dose increases with the square of the accuracy, since the number of transmitted quanta must be increased by a factor f^2 for the accuracy to increase a factor f. The dose increases rapidly with wavelength, soft x-rays being strongly absorbed. As the radiation is monochromatic, the dose provided by a particular wavelength increases exponentially with the object thickness. Since the time needed for the wedges to reach their equilibrium positions is about 10 times greater for three wedges than two, the dose is highly dependent on the number of substances analyzed. Because of these various factors, it is not practical to define the dose by an equation; the actual values should be determined experimentally or calculated theoretically for a particular set of experimental conditions. With the above three-wedge system, a dose of about 50 mr is given during a thyroid iodine analysis in a 10 cm. thick object with a required accuracy of ±0.5 mg. per sq. cm. When operating with two wedges—iodine and water—and the same conditions, only 1 mr is required.

APPLICATIONS

The iodine determinations are sufficiently accurate for quantitative analysis *in vivo* of nonradioactive iodine in the thyroid. By scanning the thyroid in a lateral projection the distribution of iodine can be charted.[5] This is a tedious process, however, and in a recent clinical study it has been replaced by single point measurements over the central part of the thyroid lobes; from these it was possible when combined with radioiodine scintillation techniques to estimate the thyroid iodine to an accuracy of ±2 mg. or ±20 per cent.[4] The mean iodine content was 12.9 mg. for normal Swedish adult controls, 12.5 in cases of thyrotoxicosis and 20.4 mg. in cases of nontoxic goiter. In thyrotoxicosis, however, only a fraction of the thyroid iodine seemed to be involved in the rapid metabolism.

The transport of iodine contrast media in the body can be studied quantitatively. For instance, the liver function has been measured in the rabbit after intravenous injection of biligrafin. Some of the results were confirmed by experiments on man.[2]

Since the biligrafin is distributed in the extracellular space,[2] the volumes of the intra- and extracellular spaces in a particular region of the body can be determined. The required data are the iodine value in the region and the iodine content of the plasma (estimated *in vitro* by x-ray spectrophotometry). Both values are determined after intravenous injection of biligrafin and equilibration.

It is also possible to determine circulation times by estimation of iodine *in vivo* after injection of a contrast medium. The advantage of the x-ray method over isotope techniques is that the patient is exposed to a smaller radiation dose. Only a local dose is then given, whereas the whole body is irradiated by the isotope until it decays or is excreted.

The method is well suited for bone salt determinations. By scanning in one direction, cortical density profiles are obtained of the type shown in Figure 5. The total amount of hydroxyapatite is determined by integrating over the shaded area. It is also possible in certain cases to calculate the amount of hydroxyapatite per unit volume of cortical bone from the shape of the profile and the dimensions of the bone, measured in 2 roentgenograms taken with perpendicular projections. Hitherto these determinations have been made with only two wedges—hydroxyapatite and water. The middle section of the metacarpal bone of the thumb has been measured of normal subjects and cases of osteoporosis. The hydroxyapatite value was found to decrease inversely with age, particularly after 50 years (Fig. 6).

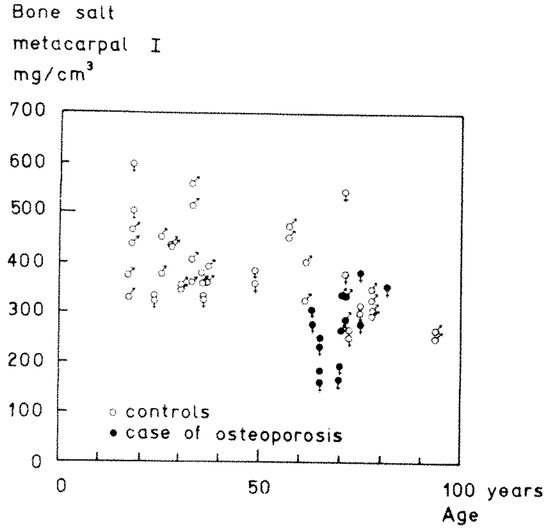

Fig. 6. Hydroxyapatite value for the metacarpal bone of the thumb decreases with the age. The values were calculated per unit volume of bone, including the marrow.

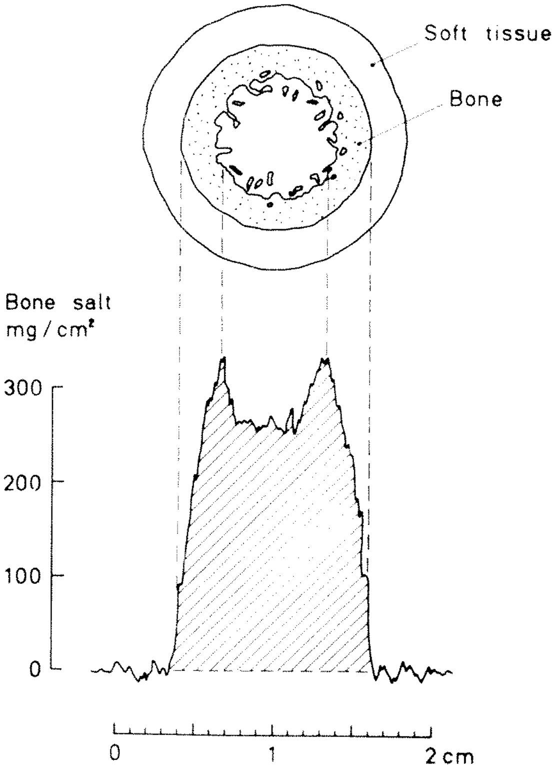

Fig. 5. Bone density profile obtained by a linear scan.

It is also possible to determine the ratio of fat to other soft tissues—for instance to distinguish edema from fat.

CONCLUSIONS

The main disadvantage of the described method in the present state of technology is the limited intensity of the monochromatic x-rays. This is a particularly difficult problem in iodine analysis when objects more than 10 cm. thick can be examined to only a low degree of accuracy. In bone salt analysis the low intensities make it difficult to use a third fat wedge, and, as pointed out above, this incurs a systematic error. Hence, further development of the technique is indicated.

The chief advantage of the described method of quantitative analysis *in vivo* is that it provides for the first time a means of solving certain problems. The technique has application in any situation in which pathologic conditions result in changes in the elementary composition in the body, or when such changes can be produced artificially, for instance by means of roentgenographic contrast media. The method is rapid, a complete quantitative analysis *in vivo* or *in vitro* requiring only a few seconds, and no preparation of the test sample is necessary. Another important advantage is that the radiation dose to which the patient is exposed is kept close to a theoretical minimum.

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Forty-sixth Annual Meeting: Greenbrier Hotel, White Sulphur Springs, W. Va., April 13–16, 1964.

EDITORIAL

THE FORTY-SIXTH ANNUAL MEETING OF THE AMERICAN RADIUM SOCIETY

THE Forty-sixth Annual Meeting of the American Radium Society will be held at The Greenbrier, White Sulphur Springs, West Virginia, April 13–16, 1964. The Society was founded in 1916 and its objectives are "to promote the scientific study of radium and other sources of ionizing radiation in relation to their physical properties, their biological effects, and their therapeutic application; and to encourage liaison between the various specialties concerned with the treatment of cancer." Its membership is comprised predominantly of radiotherapists, cancer surgeons, and radiation physicists.

All physicians and allied scientists interested in the management of cancer, especially by ionizing radiation, and those interested in the basic physical and biological aspects of ionizing radiation are welcome. They should apply directly to the Greenbrier for reservations.

The Tentative Scientific Program and Schedule of Events appear elsewhere in this issue of the JOURNAL. The Scientific Program Committee, in keeping with the expressed wishes of the membership, has invited three distinguished members of the Society to arrange symposia directed to the better understanding of the diagnosis, treatment, and statistical evaluation of cancer. Dr. John S. Laughlin has organized the symposium on "Cancer Detection by Radioisotope Scanning" which will include presentations by four outstanding workers in this field followed by a discussion period. Dr. Arthur I. Holleb has invited seven experts to participate in the symposium on "The Palliation of Advanced Cancer," each of whom will discuss the problem from the standpoint of his specialty. Dr. Antolin Raventos will chair the "Workshop on Statistics" which will cover the basic problems of production and interpretation of statistics. Representatives from the National Cancer Institute will participate in this symposium. In addition, the Committee has selected individual communications relating to the surgical, chemotherapeutic, and radiotherapeutic management of specific neoplasms as well as the basic physical and biological aspects of ionizing radiation. The Scientific Sessions will extend from 9:00 A.M. through 1:00 P.M. each day, leaving the afternoons open for group conferences and recreation. There will be no discussion of individual papers but time has been allocated for discussion periods covering groups of related papers.

One of the highlights of the Program will be an address on "Surgery and Radiotherapy—Rational Collaboration and Improved Results," by our distinguished British Guest, Dr. Frank Ellis, Radiotherapist to the Churchill Hospital, Oxford, England and President of the British Institute of Radiology.

The Janeway Lecture, always an outstanding event, will be delivered by Dr. Harold W. Dargeon, Chairman Emeritus, Department of Pediatrics, Memorial Hospital for Cancer and Allied Diseases, and Clinical Professor of Pediatrics, Emeritus, Cornell University Medical College. The title of his lecture will be "Considerations in the Treatment of Reticuloendotheliosis."

The First Executive Session of the Society will start at 2:30 P.M. on Monday in order that ample time may be provided for the discussion of several very important items of business upon which the membership will be required to vote.

Dr. Henri LeClaire, 735 Doctors Building, Cincinnati 2, Ohio is Chairman of the Arrangements Committee and he will be ably assisted by Drs. Albert L. Allen, Robert D. Berkebile, and Ralph M. Scott. The Calendar of Social Events will include a reception for all registrants by the Radium Chemical Company immediately following the Janeway Lecture on Tuesday evening. On Wednesday evening the regular reception for members and guests of the Society will be followed by the Annual Banquet and presentation of the Janeway Medal. Entertainment and dancing will follow.

The Greenbrier offers unparalleled facilities for gracious living and recreation. It is operated on the American Plan with individually decorated guest rooms and suites available as required. Equally attractive are its lovely public rooms and dining salons. The Cameo Ballroom is open for dancing every evening except Sunday and first run movies are shown each evening in the theater. Since the early part of the nineteenth century, many generations of visitors have come to this famous spa for its warm sulphur mineral baths. A wide variety of sports activities are offered by The Greenbrier including golf, tennis and both indoor and outdoor swimming in pools. In addition, cycling, horse back riding, skeet and trap shooting are available to all registrants.

Transportation to The Greenbrier, White Sulphur Springs, West Virginia, may be arranged either by train or air. The Chesapeake and Ohio Railroad offers through sleeping car service from New York, Philadelphia, Washington, Chicago, Cincinnati and Detroit. Individuals flying from the South, East, or Northeast should route into Roanoke, Virginia, and those flying from the West, North, or Northwest should route into Charleston, West Virginia. Auto taxi service from Roanoke and Charleston to The Greenbrier is readily available. In addition, The Greenbrier Airlines, White Sulphur Springs, West Virginia, offers *Non-Scheduled Air-Taxi Service* from Roanoke and Charleston. Arrangements for this service should be made directly with The Greenbrier Airlines.

Registration will start in the foyer of The Greenbrier at 12:00 NOON on April 12. Application forms for reservations have been mailed to all members of the Society and they should be returned promptly to The Greenbrier in order that both the hotel and the Arrangements Committee may anticipate the number of registrants as far in advance of the meeting as possible. Registration will be automatic upon the receipt of your confirmed reservation inasmuch as the Arrangements Committee will receive a copy of each reservation from the hotel. Scientific Guests will be charged a nominal registration fee.

The officers of the American Radium Society cordially invite you to attend the Forty-sixth Annual Meeting at The Greenbrier.

CHARLES G. STETSON, M.D.
President, American Radium Society

Mount Sinai Hospital
New York 19, New York

* * *

AMERICAN RADIUM SOCIETY

TENTATIVE PROGRAM

The following is the tentative program arranged by the Scientific Program Committee for the Forty-sixth Annual Meeting of the American Radium Society to be held at The Greenbrier, White Sulphur Springs, West Virginia, April 13–16, 1964.

Sunday, April 12, 1964

9:00 A.M.–4:00 P.M.
Executive Committee Meeting.

12:00 NOON–6:00 P.M.
Registration.

Monday, April 13, 1964

8:30 A.M. Registration—onward.

9:00 A.M.
Opening Ceremonies and Welcome Address.
Charles L. Goodhand, M.D., President, West Virginia State Medical Association, Parkersburg, West Virginia.

9:05 A.M. Address.
Charles G. Stetson, M.D., President, American Radium Society, Mount Sinai Hospital, New York, New York.

FIRST SCIENTIFIC SESSION
Juan A. del Regato, M.D., Chairman.
Penrose Cancer Hospital, Colorado Springs, Colorado.

9:15 A.M.
The Comparative Place of Irradiation and Surgery in Treatment of Bronchogenic Cancer. John L. Pool, M.D., Francisco Alaniz, M.D.,* Basil S. Hilaris, M.D.,* and Ulrich K. Henschke, M.D., Ph.D., Memorial Hospital, New York, New York.

9:30 A.M.
Radiographic and Pathologic Correlation As a Guide to Operability in Post-Irradiated Lung Cancer Patients. Morton M. Kligerman, M.D., M. Peter Scibetta, M.D.,* Charles B. Carrington, M.D.,* Samuel Hellman, M.D.,* and Richard H. Greenspan, M.D.,* Yale University School of Medicine, New Haven, Connecticut.

9:45 A.M.
Results of Radiotherapy in Patients with Inoperable Carcinoma of the Lung Whose Status Was Established at Exploratory Thoracotomy. Ruth J. Guttmann, M.D., Francis Delafield Hospital, New York, New York.

10:00 A.M.
Radiation Injury of the Lung. Bernard Roswit, M.D., and Harold M. Jones, M.D.,* Veterans Administration Hospital, Bronx, New York.

10:15 A.M.
Discussion of Previous Papers.

10:30 A.M.
Recess.

10:45 A.M.
The Potentialities for Fast Neutron Beam Radiotherapy. J. Robert Andrews, M.D., National Cancer Institute, Bethesda, Maryland.

11:00 A.M.
A Compact Radium Safe Employing Gas Sterilization. Milford D. Schulz, M.D., Edward W. Webster, Ph.D.,* and E. Theodore Agard, M.Sc.,* Massachusetts General Hospital, Boston, Massachusetts.

11:15 A.M.
Mammography As an Aid in Detection of Cancer of the Breast. Robert L. Egan, M.D.,* Methodist Hospital, Indianapolis, Indiana.

11:30 A.M.

Symposium:

Cancer Detection by Radioisotope Scanning. John S. Laughlin, Ph.D., *Chairman*, Memorial Hospital, New York, New York.

Clinical Evaluation of an Improved Method of Large Organ Scinti-Scanning for Neoplastic Disease. John P. Storaasli, M.D., Western Reserve School of Medicine, Cleveland, Ohio.

Diagnosis of Neoplastic Lesions of the Brain. Edward B. Schlesinger, M.D.,* Neurological Institute, New York, New York.

Detection and Study of Neoplastic Lesions in Bone. Ernest Greenberg, M.D.,* Memorial Hospital, New York, New York.

Dynamic Scanning of Radioactive Isotopes in Organs. Merrill A. Bender, M.D.,* Roswell Park Memorial Institute, Buffalo, New York.

1:00 P.M.
Adjournment of First Scientific Session.

2:30 P.M.–4:00 P.M.
First Executive Session—for All Members.

Tuesday, April 14, 1964

SECOND SCIENTIFIC SESSION
John L. Pool, M.D., Chairman.
Memorial Hospital, New York, New York.

9:00 A.M.
The Life History of Malignant Melanoma. Gordon P. McNeer, M.D., Memorial Hospital, New York, New York.

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* By invitation.

* By invitation.

9:15 A.M.
Recurrent Recto-Sigmoid Carcinoma—Some 2 Mev. Roentgen-Ray Results and a Bowel Protecting Technique. Magnus I. Smedal, M.D., and Kenneth A. Wright, M.S.,* Lahey Clinic, Boston, Massachusetts.

9:30 A.M.
The Superior Mediastinal Syndrome in Children with Cancer. Giulio J. D'Angio, M.D., Sidney Farber, M.D.,* and Audrey E. Evans, L.R.C.P. & S., E.,* Children's Hospital Medical Center, Boston, Massachusetts.

9:45 A.M.
Fever As a Complication of Radiation Therapy for Carcinoma of the Cervix. Martin Van Herik, M.D., Mayo Clinic, Rochester, Minnesota.

10:00 A.M.
Selected Use of Irradiation and Operation to Treat Cancer of the Cervix. Felix N. Rutledge, M.D., and Gilbert H. Fletcher, M.D., M. D. Anderson Hospital, Houston, Texas.

10:15 A.M.
Discussion of Previous Papers.

10:30 A.M.
Recess.

10:45 A.M.
Biophysical Considerations Concerning the Existence of a Threshold for Radiation Effects. Harald H. Rossi, Ph.D., College of Physicians and Surgeons, Columbia University, New York, New York.

11:00 A.M.

Symposium:

The Palliation of Advanced Cancer. Arthur I. Holleb, M.D., *Chairman*, Memorial Hospital, New York, New York.

General Surgical Methods. Henry T. Randall, M.D.,* Memorial Hospital, New York, New York.

Neurosurgical Methods. Vernon H. Mark, M.D.,* Massachusetts General Hospital, Boston, Massachusetts.

Anesthesia Techniques. Rita Jacobs, M.D.,* Memorial Hospital, New York, New York.

Pain Control by Narcotics. Raymond W. Houde, M.D.,* Memorial Hospital, New York, New York.

Radiation Therapy Methods. Juan A. del Regato, M.D., Penrose Cancer Hospital, Colorado Springs, Colorado.

Hormonal and Non-Hormonal Chemotherapy. Michael Brennan, M.D.,* Henry Ford Hospital, Detroit, Michigan.

The Use of Hypnosis. Oscar L. Morphis, M.D., Fort Worth, Texas.

1:00 P.M.
Adjournment of Second Scientific Session.

5:00 P.M.

THE JANEWAY LECTURE

Considerations in the Treatment of Reticuloendotheliosis. Harold W. Dargeon, M.D., Memorial Hospital, New York, New York.

6:30 P.M.
Reception—Host: Radium Chemical Company

Wednesday, April 15, 1964

8:30 A.M.
Second Executive Session.

THIRD SCIENTIFIC SESSION
Justin J. Stein, M.D., Chairman.
University of California at Los Angeles Medical Center, Los Angeles, California.

9:00 A.M.
Malignant Epithelial Tumors of the Nasopharynx Gilbert H. Fletcher, M.D., M. D. Anderson Hospital, Houston, Texas.

9:15 A.M.
Radiotherapy of Malignant Tumors of the Nasopharynx—A Review of 190 Cases Treated in a Period of 30 Years. Charles B. Davidson, M.D.,* Merle W. Delmer, M.D.,* Chu H. Chang, M.D.,* and Harold W. Jacox, M.D., Presbyterian Hospital, New York, New York.

9:30 A.M.
Treatment of Epithelioma of the Oropharynx with Low Intensity Radium Needles. Charles L. Martin, M.D., and James A. Martin, M.D., Martin X-ray & Radium Clinic, Dallas, Texas.

9:45 A.M.
Combined Interstitial and External Therapy in the Treatment of Head and Neck Tumors. Fernando G. Bloedorn, M.D., University of Maryland Hospital, Balitmore, Maryland.

10:00 A.M.
Management of Residual or Recurrent Cancer following Radiation Therapy for Squamous Cell Carcinoma of the Oropharynx. Alondo J. Ballantyne, M.D., and Gilbert H. Fletcher, M.D., M. D. Anderson Hospital, Houston, Texas.

10:15 A.M.
Discussion of Previous Papers.

10:30 A.M.
Recess.

10:45 A.M.
Surgery and Radiotherapy–Rational Collaboration and Improved Results. Frank Ellis, M.D.,* Churchill Hospital, Oxford, England.

11:30 A.M.

Symposium:

Workshop on Statistics. Antolin Raventos, M.D., *Chairman*, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

The Value and Use of Tumor Registry Data.

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* By invitation.

* By invitation.

Howard B. Latourette, M.D., State University of Iowa, Iowa City, Iowa.

How Should the End Results of Cancer Therapy Be Presented? Sidney J. Cutler, Sc.D.,* National Cancer Institute, Bethesda, Maryland.

Pitfalls of Using Retrospective Data in Comparing Treatments. Marvin A. Schneiderman, Ph.D.,* National Cancer Institute, Bethesda, Maryland.

Planning the Clinical Trial. James J. Nickson, M.D., Memorial Hospital, New York, New York.

1:00 P.M.
Adjournment of Third Scientific Session.

7:00 P.M. Reception—American Radium Society.

8:00 P.M. Annual Banquet and Presentation of the Janeway Medal.

Thursday, April 16, 1964

8:30 A.M.
Third Executive Session.

FOURTH SCIENTIFIC SESSION.
Milton Friedman, M.D., Chairman.
University Hospital, New York, New York.

9:00 A.M.
Chemotherapy of Metastatic Testis Cancer. A. Ranald Mackenzie, M.D.,* and Willet F. Whitmore, Jr., M.D.,* Memorial Hospital, New York, New York.

9:15 A.M.
The Treatment of Inoperable Liver Cancer by the Intra-Arterial Infusion of Chemotherapeutic and Radioisotopic Agents. Irving M. Ariel, M.D., and George T. Pack, M.D., Pack Medical Foundation, New York, New York.

9:30 A.M.
Clinical Therapeutic (Radioactive) Lymphangiography. Edwin J. Liebner, M.D.,* University of Illinois, Chicago, Illinois.

9:45 A.M.
Regional Oxygenation and Radiation—Current Status. John T. Mallams, M.D., G. A. Balla, M.D.,* and J. W. Finney, M.S.,* Baylor University Medical Center, Dallas, Texas.

10:00 A.M.
Treatment of Carcinoma of the Bladder by Supervoltage Radiotherapy. Robert H. Sagerman, M.D.,* Malcolm A. Bagshaw, M.D., and Henry S. Kaplan, M.D., Stanford University Medical Center, Palo Alto, California.

10:15 A.M.
Discussion of Previous Papers.

10:30 A.M.
Recess.

10:45 A.M.
Iridium 192, a Radium Substitute. Norman Simon, M.D., Mount Sinai Hospital, New York, New York.

11:00 A.M.
Evaluation of Tolerance and Effectiveness of the Co^{60} Moving Strip. Luis Delclos, M.D.,* M. D. Anderson Hospital, Houston, Texas.

11:15 A.M.
Experience with High Energy Electron Beam Therapy. Charles Botstein, M.D., and R. J. Schulz, M.Sc.,* Montefiore Hospital, Bronx, New York.

11:30 A.M.
The Diagnosis and Treatment of Malignant Synovioma. Milton Raben, M.D.,* Ralph Phillips, M.D., and Norman L. Higinbotham, M.D.,* Memorial Hospital, New York, New York.

11:45 A.M.
Radiation Hepatitis. John Ingold, M.D.,* George B. Reed, M.D.,* Henry S. Kaplan, M.D., and Malcolm A. Bagshaw, M.D., Stanford University Medical Center, Palo Alto, California.

12:00 NOON
Discussion of Previous Papers.

12:15 P.M.
Experience with 883 Patients with Malignant Lymphoma. David W. Molander, M.D.,* and George T. Pack, M.D., Pack Medical Foundation, New York, New York.

12:30 P.M.
The Effect of Radiation Therapy on the Survival Time of Women with Recurrent Mammary Carcinoma. Richard J. Kaufman, M.D.,* Florence C. H. Chu, M.D., and George C. Escher, M.D.,* Memorial Hospital, New York, New York.

12:45 P.M.
Fractionation and Other Variables in Preoperative Irradiation—Evaluation by a Simple Experimental Model. B. H. Feder, M.D., and Phyllis B. Blair, Ph.D.,* Veterans Administration Hospital, Long Beach, California.

1:00 P.M.
Final Executive Session for All Members and Installation of New Officers.

Adjournment of Forty-sixth Annual Meeting of the American Radium Society.

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* By invitation.

* By invitation.

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NEWS ITEMS

DR. WILLIAM D. COOLIDGE HONORED

Dr. William D. Coolidge, Honorary Member of the American Roentgen Ray Society and the American Radium Society, was awarded the Röntgen Plaque by the City of Remscheid-Lennep, Germany, the birthplace of William Conrad Röntgen, discoverer of X-rays. The presentation was made at the General Electric Research Laboratory, Schenectady, New York, where Dr. Coolidge invented the famous Coolidge tube, which revolutionized both diagnostic and therapeutic radiology.

On October 23, 1963 the great pioneer in science celebrated his 90th birthday.

NEW OFFICERS OF THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

At the Forty-ninth Annual Meeting of the Radiological Society of North America held November 17–22, 1963 at the Palmer House, Chicago, Illinois, the following officers were elected: *President*—Robert P. Barden, M.D., Philadelphia, Pennsylvania; *President-Elect*—Robert D. Moreton, M.D., Fort Worth, Texas; *First Vice-President*—Herbert M. Stauffer, M.D., Philadelphia, Pennsylvania; *Second Vice-President*—Robert E. Wise, M.D., Boston, Massachusetts; *Third Vice-President*—J. Richard Raines, M.D., Portland, Oregon; *Secretary-Treasurer*—Maurice D. Frazer, M.D., Lincoln, Nebraska; and *Historian*—Howard P. Doub, M.D., Detroit, Michigan. The new *Chairman of the Board of Directors* is John W. Walker, M.D., Kansas City, Missouri, and the new member elected to the *Board of Directors* is John H. Gilmore, M.D., Chicago, Illinois.

The Gold Medal of the Society was awarded to Harold O. Wyckoff, Ph.D., Silver Spring, Maryland.

The Fiftieth Annual Meeting will be held on November 29–December 4, 1964 at the Palmer House in Chicago, Illinois.

SEVENTH KIRKLIN-WEBER MEMORIAL LECTURE

Dr. James Bull, Professor of Radiology in the National Hospital, Queen's Square, London, and Director of the Institute of Neurology in the University of London, gave the seventh Kirklin-Weber Memorial Lecture at 8:00 p.m. on Thursday, October 31, 1963, in Balfour Hall, Mayo Foundation House. Dr. Bull spoke on "Intracranial Aneurysms Behaving As Space-Occupying Masses."

The Kirklin-Weber Memorial Lecture was established in 1959 in honor of Dr. Byrl R. Kirklin, head of the Section of Diagnostic Radiology in the Mayo Clinic from 1930 to 1951, who died in 1957; and Dr. Harry M. Weber, head of the same section from 1951 until his death in 1958.

THE ROCKY MOUNTAIN RADIOLOGICAL SOCIETY

The Rocky Mountain Radiological Society elected the following officers for 1964: *President*—John F. Bacon, M.D., Ames, Iowa; *President-Elect*—Morris H. Levine, M.D., Denver, Colorado; *1st Vice-President*—Warren B. West, M.D., Ogden, Utah; *2nd Vice-President*—Lester B. Shook, M.D., Fargo, North Dakota; *Secretary-Treasurer*—John H. Freed, M.D., Denver, Colorado; and *Historian*—H. Milton Berg, M.D., Bismark, North Dakota.

The next annual meeting will be held in Denver at the Brown Palace Hotel on August 20, 21, and 22, 1964.

VII SYMPOSIUM NEURORADIOLOGICUM

The VII Symposium Neuroradiologicum will be held in New York City at the Waldorf-Astoria Hotel, September 20–25, 1964.

In addition to essays on subjects of diagnostic and therapeutic neuroradiologic interest, there will be a symposium on Radiation and the Nervous System. The latter will include essays on radiobiology, effects of radiation encountered in outer space, and the use of ultrasound and radioisotopes in diagnosis and therapy.

The official languages of the Symposium will be English, French, German and Spanish. Application forms may be obtained from the President, Dr. Juan M. Taveras, Neurological Institute, 710 West 168th Street, New York 32, New York.

POSTGRADUATE COURSE IN DIAGNOSTIC RADIOLOGY

The seventh annual postgraduate course in Diagnostic Radiology will be presented by the Department of Radiology and Continuing Education in Medicine and the Health Sciences of the University of California, San Francisco Medical Center, March 4–8, 1964. It is an intensive five-day course which includes lectures, panel discussions, symposia, exhibits, and a social hour. Registrants may enroll for the full five days or by the day.

The Guest Faculty will include outstanding scientists from various parts of the country and England.

For application please write to: Dr. Seymour M. Farber, Assistant Dean, University of California Medical Center, San Francisco 22, California.

RADIOISOTOPE CONFERENCE

The second annual Oak Ridge Radioisotope Conference will be held in Gatlinburg, Tenn., April 20–22, 1964.

The conference will be sponsored by ORINS and Oak Ridge National Laboratory, in cooperation with the U. S. Atomic Energy Commission.

Sessions of the meeting, which will be held jointly in the Gatlinburg Civic Auditorium and the Riverside Motor Lodge, will be devoted to discussions of the use of radioisotopes in biology, medicine, engineering, and the physical sciences.

Inquiries about the program should be directed to Dr. Overman, Speical Training Division, Oak Ridge Institute of Nuclear Studies, P.O. Box 117, Oak Ridge, Tenn., 37831.

EVOLVING CONCEPTS IN PULMONARY DISEASE: POSTGRADUATE COURSE

This Course is sponsored by the Department of Radiology of the University of Miami School of Medicine and Jackson Memorial Hospital. It will emphasize new concepts in pulmonary roentgen diagnosis. Basic reviews and two clinicopathological sessions will also be presented.

The following topics will be covered: 1. Basic pulmonary physiopathology; 2. principles of chest interpretation; 3. localized and diffuse pulmonary emphysema; 4. interstitial pulmonary fibrosis; 5. miliary diseases of the lung; 6. pulmonary granulomas; 7. vascular lesions of the lungs; 8. pulmonary hypertension; 9. exotic pneumonopathies; 10. selected aspects of pulmonary neoplasms; 11. pediatric chest problems.

The Course will be held March 18–21, 1964 at Fontainebleau Hotel, Miami Beach, Florida.

The Faculty includes: Robert P. Barden, M.D., Philadelphia, Pennsylvania; Sabino Di Rienzo, M.D., Buenos Aires, Argentina; J. Scott Dunbar, M.D., Montreal, Qubec; Benjamin Felson, M.D., Cincinnati, Ohio; Felix G. Fleischner, M.D., Boston, Massachusetts; L. Henry Garland, M.D., San Francisco, California; Peter J. Kerley, M.D., London England; Ted F. Leigh, M.D., Atlanta, Georgia; Averill A. Liebow, M.D., New Haven, Connecticut; Isadore Meschan, M.D., Winston-Salem, North Carolina; John E. Rayl, M.D., Gainesville, Florida; and Leo G. Rigler, M.D., Los Angeles, California, guest speakers, as well as outstanding members of the Staff of the University of Miami School of Medicine. The Director of the Course is Raymond E. Parks, M.D., Professor and Chairman of Radiology, University of Miami, and the Chairman of the Registration Committee is Robert F. Feltman, M.D.

The Fontainebleau Hotel will send a room reservation form to all registrants for accommodations at special rates that will apply for the period of the Course and one week preceding and following the Course.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

THE RADIOLOGIC CLINICS OF NORTH AMERICA: RECENT CLINICAL ADVANCES IN RADIOLOGY. Volume I. Philip J. Hodes, M.D., Guest Editor. Cloth. Pp. 274, with many illustrations. W. B. Saunders Company, Philadelphia, Pa., 1963.

The newest addition to the journalistic style of writing in the field of radiology is "The Radiologic Clinics of North America;" it is the latest member of the "Clinics of North America" series and, following the pattern of its predecessors, contains within the hardbound volume systematic review articles on a variety of subjects.

The "Clinics" will be issued three times yearly. In general, each issue will be a symposium on a topic or topics by authors from a specific institution or radiologic group. This first volume is dedicated to Dr. Eugene P. Pendergrass, and has as guest editor Dr. Philip J. Hodes.

The text of the first issue contains 274 pages and is liberally illustrated. A cumulative index will be presented in each issue allowing for ready accessibility to subject matter.

An impressive array of authors have contributed to this first volume. They have reviewed the current concepts of the subject matter and elaborated on their techniques of examination and their criteria for interpretation.

If the first volume is an example of further works, "The Radiologic Clinics of North America" promises to be a practical method of keeping up-to-date on recent radiologic advances.

F. J. ARNOLDI, M.D.

RÖNTGENDIAGNOSTIK UND RÖNTGENTHERAPIE DER ERKRANKUNGEN DES ENDOKRINEN SYSTEMS. By Dr. I. Ispas and Dr. T. Roxin, Bukarest, Cloth. Pp. 275, with 116 illustrations. Price, Geb. DM 40.40. VEB Gustav Fischer, Verlag, Villengang 2 / Postschliessfach Nr. 176, Jena, Germany.

A monograph on the roentgenologic aspect of the endocrine system and its metabolic manifestations is quite timely and should have given not only the authors an opportunity and stimulation, but should also interest and fascinate many clinicians and radiologists who are concerned with the clinical matters related to this area.

The diagnostic part (author Dr. Ispas) gives a varied synopsis of the manifold diseases and abnormal conditions of the endocrine system and their roentgenographic appearance, with a brief discussion of the anatomic and physiologic background in each chapter. The description of the various conditions in which roentgen changes occur is adequately presented, but occasionally the correlation of diseases with multiple involvement of the endocrine organs is somewhat lacking in detail and is brief, presumably because of the rather strict anatomic background which guides the various chapters of this book. An excellent bibliography, with many referrals to East-European and foreign authors whose literature is not available, or at least not easily accessible, to readers in this country, complements the diagnostic section.

The therapeutic section (author Dr. Roxin) is much shorter, contains several deficiencies, and reflects ideas of past philosophy of radiation therapy and technical factors evidently due to lack of more modern facilities and equipment.

As in the diagnostic section, the therapeutic approach is anatomic, based on diseases of organs, rather than on the complex problems as they affect the endocrine system as a whole in its interrelationship with other systems. One would take issue in this country with many of the suggestions and indications for radiation therapy recommended by the author, particularly in benign diseases such as bronchial asthma, and amenorrhea of various ovarian and hormonal malfunctions—only to mention a few among many not usually considered indications for radiation therapy.

To those familiar with the German language, this book will make an interesting addition to their library.

H. PETER MUELLER, M.D.

BOOKS RECEIVED

DIAGNOSTICA RADIOLOGICA DELLE MALFORMAZIONI COGENITE DELL'APPARATO DIGERENTE. By Michele Cesarini and Pietro Gugliantini. Cloth. Pp. 415, with 159 figures. Società Editrice Universo, Via G. B. Morgagni 1, Roma, Italy, 1963.

BIBLIOGRAPHY ON THE EPIDEMIOLOGY OF CANCER, 1946–1960. Paper. Pp. 168, with more than 2,600 references. Price, $3.25. World Health Organization, Geneva, Switzerland, 1963.

STRAHLENSCHUTZ IN FORSCHUNG UND PRAXIS. Volume 3. Edited by Hans-Joachim Melching, Freiburg; Hans Robert Beck, Karlsruhe; Hans Adolf Ladner, Freiburg, and Eberhard Scherer, Essen. Cloth. Pp. 331, with some illustrations. Price, Leinen DM 58.80. Rombach & Co., 78 Freiburg im Breisgau, Postfach 1349, Rosastrasse 9, Germany, 1963.

STUDIES IN ANGIOGRAPHIC TECHNIQUE. By Tord Olin, from the Roentgendiagnostic Department and the Institute of Physiology, University of Lund, Lund, Sweden. Paper. Pp. 110, with some illustrations. Håkan Ohlssons Boktryckeri, Lund, Sweden, 1963.

CALCIFICATIONS OF THE HEART. By Jerome H. Shapiro, M.D., Attending Radiologist, Division of Diagnostic Radiology, Montefiore Hospital, and Associate Clinical Professor of Radiology, New York University Medical Center, New York; Harold G. Jacobson, M.D., Chief of the Division of Diagnostic Radiology, Montefiore Hospital, and Professor of Clinical Radiology, New York University Medical Center, New York; Berta M. Rubinstein, M.D., Associate Radiologist, Division of Diagnostic Radiology, and Assistant Clinical Professor of Radiology, New York University Medical Center, New York; Maxwell H. Poppel, M.D., Professor and Chairman, Department of Radiology, New York University Medical Center, Director, Departments of Radiology, Bellevue and University Hospitals, and Consultant, Division of Diagnostic Radiology, Montefiore Hospital, New York; John B. Schwedel, M.D., Attending Physician, Cardiology, Medical Division, Montefiore Hospital, and Assistant Clinical Professor of Medicine, Columbia University, College of Physicians and Surgeons, New York; and A Contribution on Cineradiography by Joseph Jorgens, M.D., Ph.D., Chief, Radiology Service, Veterans Administration Hospital, Minneapolis, and Professor in Radiology, University of Minnesota Medical School, Minneapolis. Cloth. Pp. 198, with many illustrations. Price, $12.50. Charles C. Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill., 1963.

RADIATION EFFECTS IN PHYSICS, CHEMISTRY AND BIOLOGY. Proceedings of the Second International Congress of Radiation Research, Harrogate, Great Britain, August 5–11, 1962. Edited by Michael Ebert, Paterson Research Laboratories, Christie Hospital and Holt Radium Institute, Withington, Manchester; and Alma Howard, British Empire Cancer Campaign, Research Unit in Radiobiology, Mount Vernon Hospital, and the Radium Institute, Northwood, Middlesex. Cloth. Pp. 510. Price, $15.00. Year Book Medical Publishers, Inc., 35 East Wacker Drive, Chicago, Ill., 1963.

PROGRESS IN GYNECOLOGY. Volume IV. Edited by Joe V. Meigs, M.D., Emeritus Professor of Gynecology, Harvard Medical School; Visiting Consulting Surgeon, Massachusetts General Hospital; Visiting Consulting Gynecologist, Vincent Memorial Hospital, Boston; and Somers H. Sturgis, M.D., Surgeon (Gynecology), Peter Bent Brigham Hospital, Clinical Professor of Gynecology, Harvard Medical School, Boston. Cloth. Pp. 676, with many illustrations. Price, $16.75. Grune & Stratton, Inc., 381 Park Avenue South, New York 16, N.Y., 1963.

ZAHNÄRZTLICHE RÖNTGENOLOGIE. By Dr. med. dent. Eberhard Paerschke, komm. Chefarzt der Zahn- und Kieferklinik der Medizinischen Akademie Erfurt; and Medizinalrat Dr. med. Rolf Dietze, Chefarzi des Strahleninstitutes und der Strahlenklinik der Kreiskrankenanstalten Gotha. Cloth. Pp. 154, with 176 illustrations. Price, Geb. DM 19.80. VEB Gustav Fischer Verlag, Jena, Villengang 2 / Postschliessfach Nr. 176, Germany, 1963.

DIFFERENTIALDIAGNOSE KONGENITALER HERZFEHLER: SYNOPSIS VON RÖNTGENBILD, ELEKTROKARDIOGRAMM UND PHONOKARDIOGRAMM. By Dr. Nikolaus Schad, Dr. Ralph Künzler, and Dr. Teoman Onat, Zurich. Cloth. Pp. 450, with 259 illustrations. Price, Ganzleinen DM 110. Georg Thieme Verlag, Herdweg 63, Stuttgart-N / Germany, 1963. In the U.S.A. and Canada, Intercontinental Medical Book Corp., New York 16, N.Y.

NEUTRON DOSIMETRY. Volume I. Proceedings of the Symposium on Neutron Detection, Dosimetry and Standardization held by The International Atomic Energy Agency, Atomic Energy Research Establishment, Harwell, England, December 10–14, 1962. Paper. Pp. 653, with many figures. Price, $13.00. International Atomic Energy Agency, Vienna, 1963. In the U.S.A. and Canada, International Publications, Inc., 317 East 34th Street, New York 16, N.Y.

NEUTRON DOSIMETRY. Volume II. Proceedings of the Symposium on Neutron Detection, Dosimetry and Standardization held by The International Atomic Energy Agency, Atomic Energy Research Establishment, Harwell, England, December 10–14, 1962. Paper. Pp. 615, with many figures. Price, $13.00. International Atomic Energy Agency, Vienna, 1963. In the U.S.A. and Canada, International Publications, Inc., 317 East 34th Street, New York 16, N.Y.

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ROENTGEN DIAGNOSIS

Head

Strain, Richard E. Progressive communicating hydrocephalus following subarachnoid bleeding—a neurosurgical emergency. *South. M. J.*, June, 1963, *56*, 613–618. (From: Division of Neurosurgery, University of Miami School of Medicine, Miami, Fla.)

Progressive deterioration following subarachnoid hemorrhage should suggest a complicating communicating hydrocephalus. Early recognition and proper neurosurgical shunt may be life-saving. Untreated, there is progressive neurologic deficit and death may follow. This entity constitutes a real neurosurgical emergency.

The surgical shunt, although life-saving, does not need to be permanent as pointed out by the author's first of 2 cases. Presumably new channels of absorption form or old ones begin to function again and the surgical shunt is not further necessary.

In the past this entity has not been recognized and the deteriorating course has been ascribed to nonspecific delayed effects of the original lesions, cerebral thrombosis or spasm following operation, instead of the progressive hydrocephalus.—*H. Robert Hittner, M.D.*

Poznanski, Andrew K., and Manson, Gordon. Radiographic appearance of the soft tissues in the diencephalic syndrome of infancy. *Radiology*, July, 1963, *81*, 101–106. (From: Department of Radiology, and Department of Pediatrics, Henry Ford Hospital, Detroit, Mich.)

Tumors of the hypothalamic region in infants may cause a syndrome of profound emaciation, alertness, and euphoria. This is the diencephalic syndrome of infancy, first described by Russell in 1951. The infants are usually normal at birth, and muscular development and linear growth are unaffected. The marked emaciation contrasts strikingly with the bright, alert expression and a certain degree of euphoria. Awareness of the condition is important as frequently no signs of central nervous system disease are present until the later appearance of increased intracranial pressure.

The authors have observed 4 cases of this syndrome; in all 4 there was complete absence of subcutaneous fat. Roentgenograms of the extremities showed a soft tissue shadow of uniform density without any fat lines, even in 1 patient whose roentgenograms were obtained at low kilovoltage (30 kv.) with an industrial film for maximal contrast. This has not been observed by the authors in any other condition, although it could conceivably occur in victims of extreme starvation.—*Ralph Bowman, M.D.*

Neck and Chest

Sneider, Stanley E., Winslow, Oliver P., Jr., and Pryor, T. Hunter. Cervical diskography: is it relevant? *J.A.M.A.*, July 20, 1963, *185*, 163–165. (Address: Dr. S. E. Sneider, 8900 SW 88th Street, Miami 56, Fla.)

Injection of an opaque medium such as diodrast into cervical intervertebral disks for roentgenographic study of the disks was reported by Smith and Nichols in 1957. The reliability of the diagnostic procedure has been doubtful. In an attempt to relate the symptoms of patients with neck injuries to diskography findings, the authors have studied the hospital charts and roentgenograms of 56 patients.

A total of 121 disks had been injected in patients ranging in age from 20 to 60 years. In the older age group 100 per cent of the disks studied were abnormal. In only 1 patient were all the disks injected normal. Extravasation of the contrast medium often occurred on the side opposite the symptoms. It was apparent that cervical disk disease is very common and is almost as prevelant in patients without symptoms as in those with symptoms.

Diskography has little value in studying the symptoms which persist following neck trauma.—*Richard E. Kinzer, M.D.*

Ring, B. Albert, and Eddy, Winston M. Calcification of carotid arteries: routine radiographs of the chest. *J.A.M.A.*, June 15, 1963, *184*, 866–869. (Address: Dr. B. A. Ring, Mary Fletcher Hospital, Burlington, Vt.)

With proper technique the standard 6 foot posteroanterior roentgenogram of the chest usually yields satisfactory soft tissue detail of the cervical portion of the carotid arteries. This provides the basis for studying calcification of the carotid arteries.

The authors reviewed 1,000 random cases of persons over 40 years of age and found 216 individuals with carotid artery calcification. For corresponding age groups the calcification was more frequent in males than in females.

In individuals over 80 years of age aortic arch calcification is practically universal and carotid artery calcification is found in 70 per cent.

The calcification in the cervical portion of the carotid artery is roentgenographically more readily visualized because of its anatomic location, a portion of the common carotid artery and of the carotid sinus lying in the soft tissue free of bone structures.

The significance of calcification of the cervical portion of the carotid artery in any individual case must be considered in light of the frequency with which this is to be expected in that particular age group.

Extracranial calcification is usually found in the carotid sinus which is an area most prone to degenerative change. The common carotid artery bifurcates at the level of C3 interspace. Roentgenograms including the upper border of C4 will in most instances show the area of the carotid sinus.

The carotid artery calcification was bilateral in the majority of instances.

Carotid calcification in the absence of aortic calcification was uncommon. Since the aortic arch and the carotid sinus are possible sites of turbulent flow, similar factors of degenerative change leading to calcification may be present in both.—*Edwin R. Davis, M.D.*

Sutton, David, and Samuel, Richard Harvey. Thoracic aortography in intra-lobar lung sequestration. *Clin. Radiol.*, July, 1963, *14*, 317-321. (From: Radiological Department, St. Mary's Hospital, London, W.2, England.)

The authors describe 2 cases of intralobar lung sequestration in which the diagnosis was confirmed by thoracic aortography, and a third case where thoracic aortography ruled out sequestration. They state that the left lower lobe is affected twice as often as the right, other lobes being rarely involved.

Plain roentgenograms of the chest reveal a rounded opacity usually situated in the area normally occupied by the posterior basal segment of the lower lobe. Should the sequestrated portion of the lung communicate with the bronchial tree, cavitation may occur. Thoracic aortography in the presence of a sequestration of the lung will disclose an anomalous vessel arising from the aorta, of large size, up to that of a renal artery, supplying the involved area.

Most of the patients are seen while still young, usually before the age of thirty. Should these patients come to surgery, accidental section of the anomalous artery may lead to severe or even fatal hemorrhage. This indicates the importance of thoracic aortography in the diagnosis and preoperative investigation of such lesions.—*Samuel G. Henderson, M.D.*

ABDOMEN

Fischer, K. P. Wie zuverlässig ist heute die orale Cholezystographie? (How dependable is oral cholecystography today?) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, April, 1963, *98*, 461-465. (Address: Sofienstrasse 6, Baden-Baden, Germany.)

Intravenous cholecystography with biligrafin is in some ways superior to the oral methods. There are, however, definite disadvantages. The risk of complications is bigger and the examination is more time consuming.

For a few years tri-iodated oral contrast media have been available.

In 782 patients, biloptin (Schering) was used as the oral cholecystographic medium with the purpose to compare the results with the efficiency of biligrafin. Ninety eight per cent of the normal gallbladders filled at the first oral examination. A repeat cholecystography in the nonfunctioning group with biligrafin added only 2 per cent of normal functioning gallbladders.

The efficiency quotient of the oral method therefore as far as filling is concerned was 99.7 per cent.—*Hans W. Hefke, M.D.*

Beck, Ivan T., Lacerte, Marcel, and Rona, George. Thermal injury of the stomach following intragastric colour cinematography. *Canad. M. A. J.*, Aug. 3, 1963, *89*, 216-218. (From: Department of Medicine [Subdepartment of Gastroenterology] and the Department of Pathology, St. Mary's Memorial Hospital, Montreal, Quebec, Canada.)

Development of a new gastroscope with excellent light transmission has made it possible to photograph the stomach in color. The authors report a complication which has not been noted previously.

The patient had had hematemesis. Roentgenographic examination of the duodenum suggested an ulcer crater with a possible space-occupying lesion surrounding this. No other abnormalities were seen.

Endoscopic examination was performed. The fibrescope could not be passed beyond the pylorus and the duodenal lesion could not be inspected. An erosion in the fundus of the stomach was seen and photographed. The patient did not complain of discomfort.

Laparotomy was performed the following day. A punched out ulcer of the duodenum surrounded by considerable edema was found. A subtotal gastrectomy was carried out.

The removed specimen of the stomach showed two small ulcers, one of which was felt to be the peptic ulcer seen at endoscopy. The other showed extensive coagulation necrosis of the mucosa with marked capillary engorgement and inflammatory reaction. This change would be compatible with heat coagulation of the gastric wall.

The authors suggest that in view of this possibility of injury care be exercised to avoid undue heating of the head of the fibrescope, particularly during the period of taking photographs.—*George L. Sackett, Jr., M.D.*

McGee, Andrew R. Radiological examination of Meckel's diverticulum. *Canad. M. A. J.*, July, 1963, *89*, 30-31. (From: Toronto East General and Orthopaedic Hospital, Toronto, Ontario, Canada.)

This short case report emphasizes again that a roentgenologic examination carried out to demonstrate a suspected Meckel's diverticulum is an uncertain procedure. The lesion is rarely visualized on intestinal barium studies despite various series of autopsies establishing it as one of the more common intestinal abnormalities. The reported frequency of its occurrence varies from 0.5 to 1.3 per cent.

The flexibility and length of this structure predispose to torsion and narrowing of the lumen, which constitutes a serious hazard to health. In children bleeding is the most frequent symptom, while in adults obstruction and perforation are more common.

Despite the frequent failures to demonstrate it, the occasional successful identification of this abnormality warrants the relatively simple roentgenologic examination required.—*Donald M. Monson, M.D.*

FONTAINE, R., WARTER, P., WEILL, F., and WAHL, R. Les aspects radiologiques des lipomes du côlon droit. (Radiologic aspects of lipomas of the right colon.) *J. de radiol., d'électrol. et de méd. nucléaire*, June–July, 1963, *44*, 407–412. (From: Clinique chirurgicale A, Strasbourg, France.)

Lipomas may occur in any part of the colon; over half of them cause intussusception; in the others attention is usually drawn to them by palpation of a mass or by blood in the stools.

In the authors' 4 cases, 3 were in the cecum, and ileocolic intussusception occurred in all; the fourth was at the hepatic flexure, where intussusception also occurred.

In these tumors roentgenologic study is not to be limited to the barium enema examination only, as the most evocative pictures of intussusception have been seen 7 hours after the oral ingestion of barium, at which time the last ileal loop is dilated, under tension, and at a higher level than normally. If the barium enema is given at this time, it tends to reduce the intussusception, and the tumoral lacuna is seen. —*Frank A. Riebel, M.D.*

TUCKER, ARTHUR S., and IZANT, ROBERT J., JR. How serious are gastrointestinal perforations in infancy? *Radiology*, July, 1963, *81*, 112–122. (From: Departments of Radiology and Pediatric Surgery, University Hospitals of Cleveland and Western Reserve University School of Medicine, Cleveland, Ohio.)

Twenty-six infants with evidence of gastrointestinal perforation were studied by the authors. These patients were seen at the University Hospitals of Cleveland in a ten-year period, 1952 through 1961. Objective roentgen evidence of the presence of liquid, solid, or gaseous material in a body cavity was the criterion for inclusion in this study.

Sites of perforation and survivals were as follows:

	No. of patients	*No. of survivals*
Esophagus	2	2
Stomach	5	3
Duodenum	3	0
Small Intestine	6	3
Large Intestine	7	4
No site found	3	1
Total	26	13

In 3 patients, no site of perforation could be located, although 1 was carefully explored at laparotomy and in the other 2 postmortem searches were made. The most prevalent underlying factor was prematurity, in 6 patients. Four infants experienced perforation postoperatively. Three patients had perforation as a result of barium enemas.

The survival rate of 50 per cent is an encouraging indication that perforation in infancy may not be quite as serious as has previously been reported.—*A. W. Sommer, M.D.*

LEWIS, E. C. Spontaneous perforation of the colon associated with gross surgical emphysema. *Brit. J. Surg.*, Mar., 1963, *50*, 548–550. (From: Charing Cross Hospital, London, W.C. 2, England.)

The author reports a case of a 31 year old laborer with spontaneous perforation of the colon and surgical emphysema. He reviewed the literature and found only 26 cases of spontaneous perforation of the colon. He also reviewed the literature on surgical emphysema and found only 36 cases. Therefore, the occurrence of surgical emphysema following spontaneous perforation of the colon due to gross constipation in a man aged 31 years is worthy of comment. The patient was operated upon 12 hours after admission but expired about 12 hours postoperatively. No intraperitoneal perforation was found.

At autopsy the sigmoid colon was grossly enlarged being at least 10–15 cm. in diameter with a markedly thickened wall. The apex of the sigmoid loop extended to the spleen where an abscess was found around a retroperitoneal perforation between the leaves of the mesocolon. Surgical emphysema was present around the patient's neck and shoulders and in the retroperitoneal tissue.—*Roscoe E. Miller, M.D.*

FAIRGRIEVE, J. Hirschsprung's disease in the adult. *Brit. J. Surg.*, Mar., 1963, *50*, 506–514. (Address: Resident Surgical Officer, St. Mark's Hospital, London, England.)

Only a few cases of proven Hirschsprung's disease in adults have been reported in the literature. The author notes that the condition is not so uncommon as generally supposed, and presents 7 proven adult cases seen at two London hospitals in the past 10 years. Children with the milder form may remain relatively asymptomatic and the Hirschsprung's disease may go unrecognized until adult life. Why the lesion remains undetected in some children when the majority develop serious symptoms at an early age is unknown, and apparently is not directly related to the length of the aganglionic segment.

The age range was from 17 to 36 years; and all 7 cases were males, which is in accordance with the recognized male predominance in children. No family history of similar difficulty was present.

The clinical criteria for the diagnosis of adult Hirschsprung's disease are: (1) long-standing constipation since birth or early infancy; (2) abdominal distention and often palpable fecal masses in a patient who is in good general condition; (3) rectal examination and sigmoidoscopy may reveal megarectum, or the rectum may appear normal; (4) barium enema examination shows gross megacolon and in some cases a definite coned segment. There may be delayed emptying of the colon.

The pathologic criteria are: (1) absence of the ganglion cells in both the submucosal and myenteric nerve plexuses in the distal large bowel; (2) the presence of abnormal hypertrophic nerve-fibers in both plexuses, the exact significance of which is in doubt; (3) dilatation and muscular hypertrophy of the colon above the aganglionic segment.

In all 7 cases the aganglionic segment involved only the rectum down to the level of the anal sphincter, although the lower sigmoid colon showed a reduction in the normal number of ganglion cells.

In 3 cases the rectum was dilated down to the anal sphincter, resembling idiopathic megacolon and megarectum. The preoperative diagnosis could not be made on barium enema examination, and the rectal biopsy proved of greatest value in these cases. In 3 other cases a definite narrowed rectal segment was found by barium enema study, and in the seventh case the rectum was approximately of normal caliber.

In the same 10 year period, a total of 36 cases of adult idiopathic megacolon and megarectum was seen, in which no aganglionic segment could be found either following rectal biopsy or after resection of the megacolon. The incidence of idiopathic to congenital megacolon in this small series is therefore about 6:1, suggesting that the congenital form is more common than generally realized.

Some of the various possibilities of treatment of the condition are briefly discussed.—*John R. Dehner, M.D.*

MORENO, AUGUSTO H., RUZICKA, FRANCIS F., ROUSSELOT, LOUIS M., BURCHELL, ALBERT R., BONO, RUDOLPH F., SLAFSKY, S. FREDERICK, and BURKE, JEAN H. Functional hepatography: a study of the hemodynamics of the outflow tracts of the human liver by intraparenchymal deposition of contrast medium, with attempts at functional evaluation of the outflow block concept of cirrhotic ascites and the accessory outflow role of the portal vein. *Radiology*, July, 1963, *81*, 65–79. (From: Departments of Surgery and Radiology of the Saint Vincent's Hospital of the City of New York, and the New York University School of Medicine, New York, N. Y.)

A physiologic study of the outflow tracts of the liver using intraparenchymal deposition of contrast medium was developed by the authors. The technique of this procedure is presented along with the results found in normal human subjects as well as in patients with hepatic and cardiac disorders.

In the normal human subject the typical examination showed one or more small hepatic vein branches immediately following the initiation of the deposition of the contrast medium. These branches promptly joined larger connecting trunks leading to a main hepatic vein which, in turn, delivered the medium into the inferior vena cava, where it became diluted by the large volume of blood flow in this vessel. When more than one secondary branch was seen entering a main hepatic vein, their individual jets contributed to the formation of characteristic streamlining phenomena. This streamlining and the low degree of opacification of the vascular structures were taken as an indication of the rapid rate at which blood is removed from the liver and delivered into the vena cava. Occasionally during the peak of the injecting pressure the contrast material would be forced into a portal vein branch against the normal incoming flow. This momentarily brought the incoming flow in these vessels to a standstill and produced a more dense, sharply outlined appearance. With completion of the injection, the flow in the portal branches would resume its normal direction and transport the medium into a normal sinusoidal phase.

In cirrhotic patients the travel of the contrast medium from the deposit to the vena cava occurred just as rapidly as in the normal control group. The degree of opacification of vessels and streamlining were also similar. In some cirrhotic patients an abnormal venovenous communication between the portal and hepatic vein system was noted. In an occasional rare case when obstruction of a main hepatic vein was noted the contrast material was promptly drained by other unobstructed hepatic veins that showed the rapid flow and streamlining characteristic of normal vessels, indicating compensation over the obstructive process. In cirrhotic patients with associated ascites the venous phase of medium removal was as in the other cirrhotic patients. There was, however, an unexpected removal of medium by the efferent lymphatic system of the liver in most of these ascitic patients. These lymphatic vessels were seen as tortuous, interlacing, beaded structures traversing the hepatic parenchyma to reach the hilus of the organ, the gastroduodenal ligament, and the area of the cisterna chyli. This visualization took place in cases where obstruction to hepatic outflow appeared to be as well compensated as in cirrhotic patients without ascites. In patients with an end-to-side portacaval shunt removal of the medium was as in the other patients. In those with a side-to-side shunt the removal of the contrast substance was by both the hepatic veins and the main portal vein.

In patients with congestive heart failure the hepatic veins drained the medium at a considerably slower rate, evidenced by the more marked opacification of the vessels, their sharp outline, and the complete lack of streamlining phenomena. Additionally the inferior vena cava opacified in its entire diameter and also diffused in a caudal direction to reach the level of the renal veins. Following adequate therapy correcting the congestive failure the normal drainage pattern was again seen.

The authors feel that at the present stage in these investigations it appears that intraparenchymal deposition of contrast medium may be a valid method for the functional study of the outflow tracts of the liver. The direction and speed of flow, patterns of hepatic venous drainage, alternate and accessory outflow routes amply demonstrate the hemodynamic events induced by disease. As a result of these findings new working hypotheses were formulated and a series of animal experiments were started to study the etiopathogenesis of cirrhotic and cardiac ascites. A brief discussion of these experiments is also presented.—*Donald N. Dysart, M.D.*

Freund, U., Greiling, H., and Dihlmann, W. Pseudoproteinuria after oral cholecystography. *German Med. Monthly*, July, 1963, *8*, 283–284. (From: Rheumatism Clinic and the Research Institute for Rheumatism of the State Insurance Institute of the Rhine-Province, Aachen, Germany.)

Of 23 patients examined with the oral contrast medium osbil, a substance appeared in the urine which could be identified by a test indicating proteinuria. However, further studies revealed that it was not an actual protein substance.

The authors describe several methods of examination of the urine in patients who have had gallbladder contrast medium administration. The findings of urinalysis, therefore, should be interpreted with caution if carried out shortly after ingestion of these substances.—*David C. Alftine, M.D.*

Gynecology and Obstetrics

Borell, U., Fernström, I., and Ohlson, L. Diagnostic value of arteriography in cases of placenta previa. *Am. J. Obst. & Gynec.*, June 15, 1963, *86*, 535–547. (From: Women's Clinic and the Department of Diagnostic Roentgenology, Karolinska Sjukhuset, Stockholm, Sweden.)

Arteriography permits the determination of the placental position irrespective of the type of presentation, maturity of pregnancy, or the presence of polyhydramnios. In the present investigation the arteriographic diagnosis was in accord with the clinical diagnosis in the majority of the cases (97 per cent). Arteriography was performed on many patients in this series at a stage of pregnancy in which neither vaginal palpation, cystography, nor soft tissue roentgenography would have enabled the correct diagnosis to be made.

It is advisable to avoid the performance of arteriography during uterine contractions because it was found that they may prevent satisfactory filling of the intervillous spaces and this may result in incorrect interpretation of the arteriographic appearance. As uterine contractions may be painless and are then difficult to diagnose, it is expedient to give the patient a relaxant prior to the examination.

The aim was to obtain filling of the ovarian arteries in addition to the uterine arteries in cases in which placenta previa was suspected. The catheter was introduced 30 cm. instead of 17 cm. The tip of the catheter then generally lies at the level of the point of origin of the ovarian artery from the aorta. The contrast medium was a 60 per cent solution of urografin; 70 ml. was injected within 2 to 3 seconds. Two anteroposterior roentgenograms of the abdomen were taken first. If intervillous spaces were demonstrated within the true pelvis another 70 ml. of the contrast medium was injected and the lateral roentgenogram of the pelvis was taken.

The lateral roentgenogram is of the utmost diagnostic importance since it determines whether the placenta is implanted on the anterior or posterior wall. Knowledge of this point is essential for the localization of the lower boundary of the placenta within the lower uterine segment.

Maternal mortality was nil, and the perinatal death rate was 17 per cent.—*E. J. McDonald, M.D.*

Martin, Richard D., and Matthews, Glenn B. Uterine phlebography in 2 cases of abdominal pregnancy. *Am. J. Obst. & Gynec.*, June 15, 1963, *86*, 530–534. (From: Department of Obstetrics and Gynecology, Baylor University College of Medicine and Jefferson Davis Hospital, Houston, Tex.)

Two cases of abdominal pregnancy are presented in which uterine phlebography was performed immediately prior to operation to confirm the clinical diagnosis.

The authors point out that evidence of fetal death must be present, both clinically and roentgenographically, before attempting uterine phlebography.

They state emphatically that they do not recomment the routine use of the uterine phlebography in the diagnosis of a suspected case of abdominal pregnancy. In these 2 cases, the procedure was performed because of interest in uterine phlebography.

The technique for this procedure has been described by others and is not described in this article. —*E. J. McDonald, M.D.*

RAMSEY, ELIZABETH M., CORNER, GEORGE W., JR., and DONNER, MARTIN W. Serial and cineradioangiographic visualization of maternal circulation in the primate (hemochorial) placenta. *Am. J. Obst. & Gynec.*, May, 1963, *86*, 213–225. (Address: 115 W. University Parkway, Baltimore 10, Md.)

The authors have studied maternal circulation in the primate placenta (rhesus monkey) during various stages of gestation by means of retrograde aortography. They believe that the results of this study have direct application to the human placenta.

Maternal blood was demonstrated, by cineradiography, to enter the intervillous space from the endometrial spiral arterioles, not all of which are patent simultaneously. Flow of blood into the intervillous space is regulated primarily by intrauterine pressure (strong contractions may totally impede blood flow through the spiral arterioles); the pattern of uterine contractility; and the contour of the individual contraction wave. The mixture of blood in the intervillous space was demonstrated to be nonhomogenous.

The following clinical applications have been suggested: (1) during uterine angiography, "any placenta failing to show characteristic patterns of arterial entry to the intervillous spaces must have been roentgenographed during a phase of uterine contraction or else must be the seat of extensive pathology"; and (2) biochemical analysis of intervillous space blood and placental blood removed during labor must be undertaken in light of the knowledge now available regarding placental circulation and its relation to uterine contraction.—*John H. Harris, M.D.*

CUTHBERT, R., and SPEIRS, A. L. Thalidomide induced malformations—a radiological survey. *Clin. Radiol.*, April, 1963, *14*, 163–169. (From: Stirling Royal Infirmary and Falkirk and District Royal Infirmary, Scotland.)

Malformations occurring in 16 babies born of mothers who had taken thalidomide between the 38th and 54th days after the first day of the last menstrual period are summarized. Of the 16, 6 survived, 3 were still born, and 7 lived for a period of 3 to 7 days after birth.

Features which are regarded as characteristic of the thalidomide syndrome include the following:

1. Triangular shaped scapulae with long scapular spines resulting from nondevelopment of the lateral bar and blade of the scapula, glenoid and coracoid processes. The absent areas of bone are the sites of origin of limb muscles having attachment to the humerus—teres major and minor, infraspinatus, subscapularis, biceps and coraco-brachialis.
2. Bilateral absence of radius and thumb, with manus varus deformity.
3. Absence of the superior and inferior pubic rami and symphysis, and no evidence of acetabular formation. Innominate bones and ischia show an inverted appearance. Absent areas of bone in the pelvis are the sites of origin of muscles normally inserted into the femur—pectineus and the adductors.
4. Apparent absence of femora and fibulae with fore-shortening of the extremity and thickening of pelvic tissues.
5. Femora represented by short masses of bone of rectangular shape.
6. Flexion deformity of the feet related to absent fibulae.
7. Bowing and angulation of the long bones, with skin dimples present over the angles.

It is thought that many of the deformities may be explained by a defect in outgrowth or migration of mesenchyme, from which the limbs, auricles, appendix, septa of the ventricles and truncus arteriosus all develop. Another possibility is that thalidomide may interfere with the motor neurones, and so have a dystrophic action on the migratory developing tissues of the limb.—*Samuel G. Henderson, M.D.*

RICHART, RALPH, and BENIRSCHKE, KURT. Holoacardius amorphus: report of a case with chromosome analysis. *Am. J. Obst. & Gynec.*, June 1, 1963, *86*, 329–332. (From: Division of Academic Pathology, Department of Pathology, Medical College of Virginia, Richmond, Va., and the Department of Pathology, Dartmouth Medical School, Hanover, N. H.)

Severe congenital anomaly syndromes have been described in recent years in association with chromosomal aberrations, most commonly trisomy of one of the autosomes. It is currently held that these chromosomal aberrations are directly responsible for the abnormal development. Because of the type and severity of this acardiac malformation, it was well suited to be included in a list of diseases whose possible etiology may lie in observable changes in chromosome number or morphology.

Forty-six normal chromosomes were found in mitoses of cells in a tissue culture obtained from an acardiac monster. This finding is interpreted as supporting the concept that this anomaly is secondary to chance vascular communications in the placenta. The XY sex chromosomes correspond to the sex of the associated normal twin and support previous findings of isosexual relations of such twins.

Four well-spread complete plates were obtained, photographed and karyotyped. In each plate the chromosome number was 46 and the karyotype was indistinguishable from that of a normal male. The chromosomes of the normal twin were not examined. —*E. J. McDonald, M.D.*

Heinen, G., and Schüssler, R. A new method of uterine phlebography and its diagnostic significance. *German Med. Monthly*, July, 1963, *8*, 271–273. (From: Gynaecological Department and the Radiological Institute of the University of the Saarland, Homburg/Saar, Germany.)

Contrast studies which depict the course of the pelvic vessels are useful in the diagnosis of gynecologic disorders. A visceral and a parietal venous sytem is described. The parietal venous sytem of the pelvis may be demonstrated with facility by several methods; *i.e.*, injection via the leg veins, vena cava, hemorrhoidal veins, or by the intra-osseous route into the pubis, ischium, or iliac crest. However, the vasculature of the internal genital organs is not optimally demonstrated by these techniques; satisfactory phlebograms of the visceral portion of the pelvic system are best achieved by the injection of the contrast material directly into the uterine wall. The authors have devised an instrument for this procedure which is described and illustrated. The features of the apparatus assure even, symmetric venous filling and reduce the hazard of uterine perforation.

After a uterine sounding, the instrument is adjusted so that the 4 needles penetrate the myometrium to a depth of 3 to 5 mm. Tissue permeability is increased by the instillation of hyaluronidase, and then 20 ml. of a 45 per cent solution of urografin is injected slowly. One film is exposed near the end of the injection period, another 20 seconds later.

This technique is most useful in the diagnosis of gynecologic disorders which affect the venous system of the internal genitalia such as pelvic varicoceles which are characterized by symptomatic varicosities in and about the broad ligament. So called "pelvic congestion," related to neuromuscular and vascular dysfunction, is usually manifested by increased venous filling and retarded emptying of uterine veins. This disorder may also be assessed by this method. The procedure helps in the evaluation of pelvic tumors and serves to differentiate uterine from ovarian masses. The use of pelvic visceral phlebography in patients with suspected thrombosis would seem to be of great dignostic value, but the authors have considered the procedure too hazardous to attempt.

Certain pitfalls in the evaluation of the phlebograms are described. Spurious abnormalities may be produced by the layering phenomen or by vascular spasm. Transient venous obstruction due to uterine contraction is occasionally encountered. The use of general anesthesia and spasmolytic agents improves the technical quality of the study.

There are illustrations depicting the appearance of the normal uterine phlebogram and examples of various pathologic states.—*Jack Reynolds, M.D.*

GENITOURINARY SYSTEM

Winter, Chester C., and Beyer, John. Surgical renography. *J. Urol.*, May, 1963, *89*, 755–758. (From: Division of Urology, Department of Surgery, Ohio State University Medical Center, Columbus, Ohio.)

With certain modifications, standard isotope renography for the determination of kidney function can be accomplished during surgical procedures upon the kidneys. Using hippuran taged with I^{125} instead of the customary I^{131}, the authors have been able to adapt a small transistorized scintillation counter with a crystal, 0.2 cm. thick and 1.2 cm. in diameter, and an oval brass collimator, 2 mm. thick. This collimator can be adapted to cover one-third to the entire kidney. With 2 or 3 similar probes lashed together individual segments of the kidney can be tested.

In practice, during surgery, these probes are covered by a sterile plastic bag. The probes are connected to a recorder through a rate meter, which will allow a strip chart tracing for 15 to 20 minutes.

Surgical renography by this method has been performed in 24 patients and examples of the tracings are included in this article. Only one renogram in this series corresponded to the conventional normal renogram tracing in that it showed the three phases: the initial vascular spike, the secondary functional rise, and the terminal evacuation segment. The remaining surgical renograms showed the first two segments but not the third within the time limitation of 20 minutes. Certain alterations of renal function and urine formation which are secondary to general anesthesia are mentioned.

Perhaps the most practical application of surgical renography is the evaluation of the contralateral kidney during surgical attack upon a diseased organ. With renography available, this may be done at the operating table.

Segmental renal disease may also be evaluated at the time of surgery and the final decision as to whether to do a total or partial nephrectomy can be made at the operating table.

Eight figures illustrate the equipment and the tracings.—*George W. Chamberlin, M.D.*

Woodruff, Marvin W., Kibler, Raymond S., Bender, Merrill A., and Blau, Monte. Hg-203 neohydrin kidney photoscan: an adjuvant to diagnosis of renal disease. *J. Urol.*, May, 1963, *89*, 746–752. (From: Departments of Urology and Nuclear Medicine, Roswell Park Memorial Institute, Buffalo, N. Y.)

The mercurial diuretic neohydrin labeled with Hg^{203} is better suited for investigation of the kidneys than I^{131} contrast media because of the binding effect of mercury to the sulfhydril group of the enzyme system found in the renal tubules. This results in a more prolonged selective concentration of the isotope within the kidneys. In addition, the small amount of Hg^{203} labeled neohydrin required for this procedure supplies a monoenergetic gamma ray emission which lends itself to better resolution of the photoscan. Patients to be scanned receive 150 μc Hg^{203} chlormerodrin intravenously. The renal photoscans are performed 2 hours following injection. This coincides with the period of maximum deposition of the isotope material within the kidney. The patient is placed in the prone position and the usual radioisotope scanner is used.

The patients studied included those with renal tumor, renal cyst, chronic renal disease, congenital anomalies, hydronephrosis, renal vascular disease, compensatory hypertrophy, calculus disease, and normal individuals.

As a result of experience in 78 patients who have been subjected to mercury photoscans as an adjuvant to the other investigations of urinary tract disease, the authors have found that this procedure is most valuable in two general groups. Patients with renal disease processes causing specific areas of renal parenchymal destruction will demonstrate an area of decreased uptake on the scan as noted particularly with tumor and vascular disease. Patients with anomalies of form, size, and number can be verified by demonstration of normal Hg^{203} neohydrin uptake thus ruling out a space-occupying lesion. Failures of this technique are primarily related to those abnormalities where there has been extensive renal function deterioration and insufficient parenchyma remaining for good renal delineation.

Ten composite figures are presented to illustrate the findings in this article.—*George W. Chamberlin, M.D.*

TARDOS, R. Etude radiologique des lésions urétérales et rénales de la bilharziose urinaire. (Radiologic study of the ureteral and renal lesions of urinary bilharziosis.) *J. de radiol., d'électrol. et de méd. nucléaire,* March–April, 1963, *44,* 187–190. (From: Service Central d'Electroradiologie de l'Hôpital du Val-de-Grâce, Toulouse, France.)

Bilharziosis is a disease caused by *Schistosoma haematobium* (Bilharzia). It is endemic in many parts of Africa, Madagascar, Egypt and certain areas in the Near East. It is also found occasionally in Southern Europe, in the south of Spain and Portugal.

The disease in France is encountered among Europeans who have been exposed to the disease while living overseas and among Africans who live in Metropolitan France. (Tropical diseases are not a rarity in the United States. They may be found among Americans who were living abroad as well as among foreigners who are traveling through or residing in this country. With a high incidence of suspicion we should be able to discover many tropical diseases among residents of the United States which otherwise pass unnoticed. Abstractor's comment.)

The *Schistosoma haematobium* enters the body by the alimentary tract, especially in drinking water or through the skin of persons bathing or wading barefooted in infested waters. The parasite gains access to the venous system and finally lodges in the wall of the urinary bladder as well as the ureters.

The submucosa of the bladder is infested with eggs of the parasite; it is studded with characteristic whitish spotty elevations as seen during cystoscopy. These may cause scar formation, fibrosis and sometimes calcification. In the ureters, however, the parasites invade not only the mucosa and submucosa but the muscularis as well. This results in alteration in the caliber, contour and course of the ureters with tortuosity, strictures, fibrosis and proximal dilatation, expecially hydronephrosis of the kidney. Calcifications may be present in the walls of the ureters.

Contrary to prevalent opinion that the parasites most frequently invade the bladder—based on a review of the recent literature as well as the experience with his own 30 cases—the author stresses the importance of involvement of the ureters. By the same token, in addition to the plain roentgenogram which may reveal calcifications along the course of the ureters or in the bladder wall, he emphasizes the importance of intravenous urography as a significant roentgenologic procedure in evaluating the renal pelvis and ureters. Examination of the bladder may be performed as part of excretion urography or by direct cystoscopy.

Eleven reproductions of selected roentgenograms from the 30 cases observed by the author accompany this article.—*William H. Shehadi, M.D.*

SOIFER, EDGAR, and MAROULIES, MILTON. Visualization of infiltrating tumors by perivesical gas insufflation. *J. Urol.,* May, 1963, *89,* 759–762. (From: Kings County Hospital, Department of Surgery, Division of Urology, Brooklyn 3, N. Y., and State University of New York, Downstate Medical Center, Department of Surgery, Division of Urology, Brooklyn 3, N. Y.)

The patient is placed on the laminagraphic table in the supine position. Intravenous demerol is used for analgesia. A catheter is inserted into the bladder and after the bladder has been drained approximately 200 to 300 cc. of air or carbon dioxide is injected. The patient's knees are flexed and a 4 inch No. 9 needle is inserted in the midline of the perineum and is directed by a finger placed in the rectum. The needle is first directed to the right, lateral to the prostate, and just distal to the bladder neck. Two hundred cc. of carbon dioxide is injected. The needle is then partly withdrawn and directed to the left lateral aspects of the prostate at the same level and another 200 cc. of carbon dioxide is injected. Two minutes later anteroposterior and oblique laminagrams are made. The carbon dioxide around the bladder is rapidly absorbed.

Of 17 patients studied in this manner, 12 had cystoscopic evidence of a bladder tumor proven by biopsy. The remaining 5 patients were controls and had no evidence of bladder tumors. By employing this technique, the authors were able to visualize intravesical protrusion and also extravesical extension of the bladder growth in 10 of the 12 patients.

The authors prefer this method to the prevesical injection of carbon dioxide, because most of the tumors are located in the bladder base or floor. They feel that this technique is probably more efficacious than the prevesical contrast injection since it results in satisfactory contrast of the bladder base as well as the posterior, lateral and anterior walls of the bladder. Carbon dioxide is used due to the fact that it is less dangerous than oxygen for prevesical injection.

Four roentgenographic reproductions and diagrams are presented to illustrate the procedure.—*George W. Chamberlin, M.D.*

Fam, Azia. Pericystitis and its simulation of malignant disease of the bladder. *Brit. J. Urol.*, June, 1963, *35*, 166–168. (Address: Cairo University, Cairo, Egypt.)

This report is from Egypt. The high incidence of bilharzial involvement of the lower urinary tract causes many cases of pericystitis which may be difficult to differentiate from malignant bladder tumors.

Bilharzial ova are first deposited in the bladder wall, and cause a foreign body reaction which extends outward into the surrounding soft tissue. Secondary infection usually occurs. The loose cellular tissue around the bladder becomes thick and fibrotic. Fistulae may develop. Bladder defects are produced which may mimic primary tumors.

The differential diagnosis is difficult. Roentgen examination may be helpful. On a plain roentgenogram the outline of the calcified bilharzial bladder shows indentations along the wall, whereas in carcinoma the calcification may be irregular, blotchy, and vary in density. Cystograms may show similar changes. A filling defect with a regular edge favors pericystitis. Cystoscopy also may be helpful or diagnostic.

In the author's series of 171 cases of pericystitis, 79 per cent were due to benign bilharzial involvement.—*George L. Sackett, Jr., M.D.*

Wightman, J. A. K. Genito-urinary aspects of Marfan's syndrome with case report. *Brit. J. Urol.*, June, 1963, *35*, 143–146. (From: The Royal Hospital, Sheffield, England.)

Marfan's syndrome (arachnodactyly, congenital subluxation of the lens, and cardiovascular abnormalities) has been explained on the basis of a hereditary disorder in the development of connective tissue. Other less constant abnormalities associated with this syndrome suggest that the causative factor may also be in the development of structures of mesodermal origin rather than connective tissues alone.

Genito-urinary abnormalities appear with considerable frequency and patients with Marfan's syndrome should probably be evaluated for such abnormalities.

If a mesenchymal disorder is responsible, abnormalities in dentition and muscular development might also be suspected and it is recommended that attention be paid to this aspect.

The author reports a 17 year old male with Marfan's syndrome who developed torsion of the testis on each side on separate occasions. Intravenous pyelograms also showed rotation of the left kidney.—*George L. Sackett, Jr., M.D.*

Wood, Colin, and Borges, Francis J. Perimuscular fibrosis of renal arteries with hypertension. *A.M.A. Arch. Int. Med.*, July, 1963, *112*, 79–91. (Address: Dr. Colin Wood, Department of Pathology, University of Maryland School of Medicine, 31 S. Greene Street, Baltimore 1, Md.)

The authors report in detail the clinical, laboratory, and pathologic findings in 3 young women with perimuscular fibrosis of the renal arteries and hypertension.

The pathologic lesion was concentric hyaline fibrosis of the outer media and external elastic layer. The fibrosis was perimuscular in each of over 500 sections of the renal arteries in these cases. The muscular layer of the markedly fibrotic arteries was thin where the fibrous band was thickest, perhaps secondary to the ischemic atrophy of the underlying muscularis. The abnormality involved the main renal arteries and extended into the primary branches, especially the anterior branch, but not into the subdivisions. One patient died a year after surgery and had the same lesion in 2 aberrant arteries to the opposite kidney, although fibrosis was not found in any other artery.

Retrograde femoral arteriography in 2 cases revealed irregularity and narrowing of the renal arteries without well-defined "beading" as seen in fibromuscular hyperplasia.

The etiology of perimuscular fibrosis remains unknown. Endocrine factors, previous arteritis, and collagen disease have been suggested but the findings in the authors' cases did not support any of these as causative agents.

The 3 patients were treated by unilateral nephrectomy. The extension of the lesion from the main renal artery into the anterior branch was a cause of difficulty in bypass grafting. There was relief of hypertension in 1 case with a 6 month history of hypertension and no evidence of involvement of the opposite kidney by radioisotope renogram or differential clearance studies.—*William J. Miller, M.D.*

ROSENTHALL, LEONARD. The usefulness of renal scanning as an adjunct to excretory urography. *J. Canad. A. Radiologists*, June, 1963, *14*, 76–83. (From: Montreal General Hospital, Montreal, Quebec, Canada.)

Renal scanning with radioactive mercury-tagged neohydrin is a rather new test, but already it has become an important one. The author has employed neohydrin labeled with Hg^{203} in his reported study. This tracer yields a rather high dose of approximately 5 rads to the kidneys with the usual tracer dose of 100 microcuries. Recent experience of a number of investigators suggests that neohydrin tagged with Hg^{197} affords information as good with considerable reduction in patient dose.

For scan studies the author has employed a commercial scanner with focusing collimator, and apparently uses a background erase circuit such as that devised by MacIntyre and Houser. His records are in the form of solenoid print scans. Areas of usefulness in the reported material include the detection of space-occupying lesions, detection of altered function, and identification of renal size and shape. Twelve cases are described, and are liberally illustrated with urograms, renal arteriograms and scans. Some of the conclusions drawn from the scans are not very well supported by the illustrations, but perhaps the material has suffered by the small size of the reproductions. Also, the roentgenograms are printed in the usual way, with the patient's right to the reader's left, while the scans are printed in the scan position with the patient's right to the reader's right. This makes it somewhat difficult to relate scan data to the roentgenograms, but despite these disadvantages the published material is of good quality, and represents a contribution to the growing literature on renal scanning which should be read by everyone who employs this interesting test.—*Frederick J. Bonte, M.D.*

KÖHLER, R. Correlation between vascular supply to the kidney and excretion as shown by urography in renal tumours. *Radiol. clin.*, 1963, *32*, 100–111. (Address: Daserng 2 B, Helsinki, Finland.)

In the diagnosis of renal tumors by urography it has been thought that there was some correlation between the amount of tumor-destroyed parenchyma and reduced concentration of the contrast medium. However, inconsistencies have been observed and the author carried out an analysis of his cases to determine this.

From 1951 to 1961, he found that there was incomplete correlation between the amount of parenchyma destroyed and the reduced contrast density in 24 kidneys of 78 cases of renal carcinoma examined urographically and at the same time angiographically. The contrast density at the juxtaureteral confluence was assessed by comparison with the other side. The amount of renal parenchymal destruction was estimated on the nephrographic phase of angiography and all cases were verified histologically.

Further analysis revealed inconsistencies in 3 groups. In the first group of cases, 3 had parenchymal destruction exceeding ¾ of the renal volume and 15 had ½ to ¾ loss of volume with unimpaired contrast density despite extensive destruction by tumor. The significant feature was that the remaining parenchyma had a good arterial supply and the outflow from the kidney was not obstructed. A second group of 4 cases showed reduced contrast despite inconsiderable tumor destruction. The reduced contrast in all these cases was caused by obstruction of the renal outflow. Secondary to the obstruction, a decrease in vascularization occurred which was not due to tumor destruction. The third group consisted of 2 kidneys which showed no excretion of the contrast medium despite only slight tumor involvement. These kidneys were also obstructed due to secondary infection and the tumors were not diagnosed preoperatively.

The conclusion is reached that renal excretion of contrast material depends not only on the quality and amount of the renal parenchyma, but also on the intrapelvic pressure and the blood flow. Consequently, slight or no excretion can occur with a small tumor and good excretion with an extensive one. Thus urography appears to have the drawback of indirect diagnosis, while angiography is capable of establishing not only the nature of the tumor but also the volume and nutrition of the unaffected renal parenchyma. The 2 cases with no excretion constituted an exception in that angiography failed to reveal the malignancies because of vascular changes secondary to stasis and infection which could not be distinguished from a very small tumor.—*A. Raymond Brooker, Jr., M.D.*

YASKY, JULIO, and VOLPÉ, ROBERT. An assessment of the "radioactive renogram" using o-iodohippurate sodium (hippuran) labelled with radioactive iodine. *Canad. M. A. J.*, May 25, 1963, *88*, 1055–1064. (From: Department of Medicine, and Isotope Laboratory, St. Joseph's Hospital, Toronto, Ontario, Canada.)

Isotope renography was first performed by Winter in 1956 using I^{131} labelled iodopyracet (diodrast). This substance was not satisfactory because some of it was taken up by the liver making localization on the right side difficult, and often yielding spurious results. Later I^{131} iodohippurate (hippuran) was employed. This is also virtually cleared from the plasma on one passage through the kidneys by combined glomerular filtration and tubular excretion, but it is not taken up by the liver.

Instrumentation for isotope renography includes 2 identical scintillation counters, count rate meters, and strip chart recorders. The examination is carried out in the prone position with the patient well hydrated. A small test dose is given and the probes are accurately localized in the renal area of highest activity. The recorders are equilibrated by suppressing background and the full test dose administered. A record is obtained for 20–25 minutes with a recorder speed of 12 inches per hour.

The record obtained has three characteristic segments: the initial uptake, the secretory segment, and the excretory phase. The initial uptake phase was previously called the vascular spike, but recent work has shown it to be more than a manifestation of vascular flow through the kidneys; functional activity of the kidneys also contributes part.

Isotope renography was performed on 57 patients with hypertension and various other diseases of the kidneys.

Significant differences from the normal curves are noted in the renograms in essential hypertension and in chronic renal disease. Moreover, in unilateral renal disease there is obvious difference between the two sides making the renogram particularly valuable in this situation.

Isotope renography is a simple, nontraumatic procedure which yields qualitative information regarding kidney function and relates the function of one kidney to the other. It is particularly applicable in the investigation of unilateral kidney disease.—*Craig C. Wetzelberger, M.D.*

NERVOUS SYSTEM

Luyendijk, W. Canalography: röntgenological examination of the peridural space in the lumbosacral part of the vertebral canal; summary of the thesis. *J. belge de radiol.*, 1963, *46*, 236–254. (Address: Prins Bernhardlaan, 60, Oegstgeest, The Netherlands.)

Canalography or peridurography is a roentgenologic procedure for the study of the size and shape of the peridural space in the lumbosacral and spinal canal area. The peridural space is located between the spinal dura mater and the walls of the spinal canal and extends from the upper cervical to the sacral level. It contains the spinal nerves, blood vessels, areolar connective tissues and fat. At its caudal end the dural sac tapers into the dura mater of the filum (filum durae matris) which extends into the sacral canal. The dural sac is connected with the paravertebral and presacral connective tissue through the intervertebral foramina. In these openings, connective tissue attaches the spinal nerves and blood vessels to the walls of the foramina. This formation is known as "Charpy's ligament."

The peridural space is punctured with a needle through the sacral hiatus and hypaque or renografin is injected. Films are exposed in the frontal, lateral and oblique projections. The contrast material surrounds the spinal cord and in the lateral view, it is visualized both anteriorly and posteriorly (ventrally and dorsally).

By means of this method prolapse of the disk, protruding disk with osteochondritic spur formation, developmental anomalies with narrowing of the lumbar vertebral canal, dilated peridural veins, peridural and/or periradicular adhesions, spina bifida occulta, hypertrophy of the ligamentum flavum, sacral perineural cysts and spondylolysis may be demonstrated.

The contrast material is rapidly absorbed and within 30 to 45 minutes it appears in the urinary tract, thus an urogram is obtained.

The author's experience is based on a study of 460 patients. The procedure was unsuccessful in only 7.8 per cent; this was due to developmental anomalies or variations of the sacral hiatus which could not be entered with the needle.

One table, 7 diagrams, 2 sketches and reproductions of roentgenograms accompany this excellent article.—*William H. Shehadi, M.D.*

Moes, C. A. F., and Hendrick, E. Bruce. Diastematomyelia. *J. Pediat.*, Aug., 1963, *63*, 238–248. (From: Departments of Radiology and Surgery, The Hospital for Sick Children and the University of Toronto, Toronto, Ontario, Canada.)

Fourteen cases of diastematomyelia collected over a 12 year period are reviewed. In 7 the diagnosis was made at autopsy. Of the remaining 7, laminectomy was performed in 6.

Diastematomyelia is a developmental defect in which the spinal cord is divided longitudinally by a fibrous or bony septum. There are two hypotheses to explain the development of the septum. One postulates inadequate re-absorption of cerebrospinal fluid after closure of the neural tube, which usually occurs between the third and fourth week. This produces secondary dilatation of the neural canal with displacement and distortion of the precursors of the vertebral column. A second theory, more widely accepted, is that of Bremer. He suggests that the changes may result from partial obliteration of an accessory neurenteric canal. This canal is a normal communication between the intestinal tract and the dorsal surface of the embryo but only lasts a short time. Its persistence as a cyst or fibrous cord is thought to eventually lead to the formation of a septum. The persistent canal is also thought to produce the associated vertebral and cutaneous anomalies.

The condition usually becomes apparent in infancy or childhood. The presenting symptoms are: difficulty in walking, failure to obtain bladder or bowel control and anomalies of the legs and feet. Six of the authors' 14 cases had associated meningoceles. Four presented with a hairy patch, 1 with a sacrococcygeal sinus and 1 with a soft tissue swelling over the base of the spine.

Roentgenographically, the spinal canal was widened at the level of the lesion in all but 1 of the authors' cases. This widening may extend over a variable number of segments. Spina bifida occulta was present in 12 of the 14 cases. Other frequently associated anomalies may be hemivertebrae, hypoplastic vertebral bodies, narrowed intervertebral disks, kyphosis and scoliosis. If the septum is not bony, myelography is extremely helpful for localization.

Laminectomy is the operation of choice with removal of the septum. Surgical correction of the defect usually prevents progression of the neurologic changes but improvement is rare.—*Barry Gerald, M.D.*

SKELETAL SYSTEM

Eggers, G. W. N., Evans, E. Burke, Blumel, Johanna, Nowlin, Donald H., and Butler, James K. Cystic change in the iliac acetabulum. *J. Bone & Joint Surg.*, June, 1963, *45-A*, 669–686. (From: Department of Surgery, Division of Orthopedic Surgery, The University of Texas Medical Branch, Galveston, Texas.)

Cystic changes in the acetabula may accompany a degenerative arthritis or occur prior to, or independent of, the degenerative joint lesions.

These cysts are usually marginal or subchondral and underlie the weight-bearing area in a plane beneath and posterior to the anterior-inferior iliac spine. In 80 cadavers with acetabular cysts there was some degree of erosion of the acetabular cartilage at the point of greatest weight bearing, but only one had changes in the cartilage of the opposing femoral head. Hips with abnormal configuration showed a greater degree of involvement than normal hips and the degenerative process was accelerated. The cystic changes may be unilateral. They vary in size and may be either multi or unilocular. The walls are sclerotic. In the larger cysts there was extension well into the ilium or even medially towards the pubic and ischial acetabular areas. Occasionally defects may be shown in the subchondral plate. Cysts near the margin may fracture with lateral displacement of the femoral head. In 122 cases of acetabular cysts, 60 showed arthritic changes in the femoral heads and 21 had cysts in the heads. Although most patients were in the older age groups, 1 was under 20, 3 in the 20–29 year range and 11 in the 30–39 year range.

The authors consider acetabular cysts to portend change in the femoral head and this has been observed in untreated patients. However, in 1 patient, treatment of the cyst did not prevent subsequent cyst formation in the femoral head. A subtrochanteric osteotomy or femoral head prosthesis may cause cysts to regress, but the authors prefer to restore the acetabulum directly. When prostheses were inserted they found that pain persisted if the cysts were not obliterated; apparently there is stress on the subchondral plate.

There are several hypotheses as to cyst development. The authors believe the formation of cysts to be secondary to friction and pressure. It is suggested, therefore, that as cartilage is destroyed through fibrillation and erosion there is hyperemia with bone resorption and replacement by fibrous tissue. Reactive bone forms and if the blood supply is insufficient there may be cavitation in the areas of fibrosis. Microfractures may also occur. Some cysts connect to the joint.

Twenty-seven painful hips with cystic acetabular lesions were treated surgically with removal of the fibrous tissue or fluid, destruction of the sclerotic cyst walls, and packing with autogenous bone. The pain had been present in these cases from a few months to 15 years, was deep-seated and often worse on weight-bearing. The follow-up period averaged 3 years 8 months. Sixteen of the patients had excellent relief of pain, 4 had partial relief and 7 had no improvement. Fair and poor results were noted in patients whose hips showed articular changes and deformity of the head. In none of the patients with normal or nearly normal heads was there recurrence of pain after surgery. Even moderately advanced degenerative changes do not contraindicate surgery since there was a significant degree of subsequent improvement in these patients.—*Martha Mottram, M.D.*

Robins, M. Moreno, Stevens, Houston F., and Linker, Alfred. Morquio's disease; an abnormality of mucopolysaccharide metabolism. *J. Pediat.*, June, 1963, *62*, 881–889. (From: Primary Children's Hospital and the Department of Pediatrics and Radiology, University of Utah College of Medicine, Salt Lake City, Utah.)

The authors describe two siblings with Morquio's disease at the age of 8 months and 3½ years. The 8 month old infant was found to have roentgenographic manifestations of the disease without clinical signs. The older girl, in addition to having the roentgenographic manifestations, had corneal opacities on slit lamp examination. Both patients had Reilly granulations in the polymorphonuclear leukocytes of peripheral blood and bone marrow. They both excreted keratosulfate, a mucopolysaccharide different from that found in the urine of normal people or in patients with Hurler's disease.

The roentgenographic bone changes are quite variable, and accurate evaluation requires longitudinal assessment. The number and degree of abnormal findings almost always accompany the appearance of secondary ossification centers and metaphyseal growth. The disorder is characterized by delayed, deficient, and irregular endochondral ossification of the epiphyses and diaphyses.

Although patients with clear cut Morquio's disease are usually readily distinguishable from gargoylism (Hurler's disease), there are borderline cases in which the differentiation is difficult. Reilly granules in the leukocytes and increased mucopolysaccharides in the urine have also been used to differentiate Hurler's disease from other hereditable diseases of connective tissue.

Both patients demonstrated Reilly bodies in the peripheral polymorphonuclear leukocytes (45 per cent and 80 per cent respectively), and an increase in keratosulfate excretion in the urine.

Other authors have stated that those patients with clinical and roentgenographic features of Morquio's disease who, in addition, have corneal opacities, deafness, Reilly granulations, and excess mucopolysaccharide in the urine should be classified separately from either Morquio's disease or Hurler's disease—as Morquio-Ullrich disease. Their review of the literature would indicate that few cases have had a search for either Reilly granulations or corneal opacities, while the more recent reports indicate that both may be present commonly in Morquio's disease. Since both these conditions are probably manifestations of abnormal mucopolysaccharide deposition, the authors believe that they could logically be included as manifestations of Morquio's disease and that the creation of a "new" syndrome is not warranted.—*James F. Martin, M.D.*

ZENER, JULIAN C., ALPERT, MEYER, and KLAINER, LAWRENCE M. Vertebral sarcoidosis. *A.M.A. Arch. Int. Med.*, June, 1963, *111*, 696–702. (Address: Dr. Meyer Alpert, Department of Radiology, The Presbyterian Hospital, Columbia-Presbyterian Medical Center, 622 W. 168th Street, New York 32, N. Y.)

The authors report a case of vertebral sarcoidosis in a 33 year old Negro female. The onset of her symptoms was in December, 1960 at which time she noticed a stabbing nonradiating mid-back pain, which increased on lateral bending of the spine. This was associated with night sweats, occasional nonshaking chills, dyspnea on climbing stairs and a cough, productive of a small amount of gray sputum, occasionally flecked with blood. The back pain increased in severity during the winter, and by March, 1961 the patient had restricted her activities to light housework.

The patient was first seen at the Presbyterian Hospital in June, 1961. There was marked tenderness over the lower thoracic spinous processes. She had a normal temperature, hemoglobin, hematocrit, white blood cell count, differential count and urinalysis. The sedimentation rate was 60 mm. per hour and the alkaline phosphatase was slightly elevated. Roentgenograms of the thoracic spine demonstrated a paravertebral soft tissue swelling extending from T 8 through T 10. The lateral roentgenogram showed moderate sclerosis of the vertebral body of T 9, predominantly along its periphery. The frontal roentgenogram revealed a slight decrease in the height of the right half of the body of T 9 and sclerotic changes in the same area. A 5 mm. lytic lesion was demonstrated in the right superior border of this vertebral body. The adjacent disk spaces were normal. Roentgenograms of the lumbar spine showed an oval ring-like zone of sclerosis in the body of L 2. There was slight decrease in the height of the left side of this body. Adjacent disk spaces were intact. The original roentgen diagnosis of the spine lesions was tuberculosis. Chest roentgenograms were negative. Five Mantoux tests were performed and these were all negative. Sputum and urine were each cultured 3 times, a 24-hour sputum was cultured and 2 guinea pigs were inoculated with urine. No organisms were recovered from these specimens. Skin tests for histoplasmosis, coccidioidomycosis and blastomycosis were negative. Craig cannula biopsies of the vertebral bodies of T 9 and L 2 were performed. The predominant microscopic findings were moderately fibrotic marrow with scattered plasma cells and reticuloendothelial cells. There were noncaseous tubercle-like structures with giant cells and epithelioid cells. The initial pathologic diagnosis was tuberculosis. A Kveim test was planted on August 4, and in September it showed no induration. On October 23 slight induration was noted and a biopsy of the Kveim test area was obtained which disclosed several granulomas within the corium, consisting of giant cells and epithelioid cells with a few lymphocytes. The histologic findings at this time were interpreted as definitely positive for sarcoidosis. The differential diagnosis considered by the authors included pyogenic osteomyelitis, tuberculosis, Hodgkin's disease and mammary carcinoma.

In summary, the authors state that only 3 cases of well-documented vertebral sarcoidosis have been diagnosed before death. In contrast to the usual lack of symptoms in the short tubular bone sarcoidosis, pain and local tenderness have been prominent features of vertebral involvement. Roentgenograms have demonstrated lytic and/or sclerotic lesions in the affected segments. Disk space narrowing and a paravertebral mass would raise the question of tuberculosis; however, the diagnosis of vertebral sarcoidosis was fairly well confirmed.—*C. Peter Truog, M.D.*

MEYER, TEARLE, GOLTER, LOWELL E., and HAWLEY, CHAPIN. Avascular necrosis of bone following systemic steroid therapy. *Radiology*, March, 1963, *80*, 422–426. (Address: The Christ Hospital, Cincinnati 19, Ohio.)

Although the common complications of steroid therapy are well known, avascular necrosis of bone and resultant joint destruction are uncommon and generally unrecognized complications. The authors present a report of such a complication following long-term steroid therapy, which was administered systemically only.

The patient, a 50 year old white woman, had had subtotal thyroidectomy in 1929, pelvic surgery in 1934 and 1938, and in 1945 a total colectomy with an ileostomy was performed for what was diagnosed elsewhere as an "elongated, atrophic, atonic colon." She had been taking desiccated thyroid daily since 1934. Episodic thromobocytopenic purpura first appeared in 1957 and in 1958 a repeat episode prompted daily aristocort therapy from April until November. Following a fall on her buttocks in December, 1958, the patient was hospitalized and roentgenographic examination revealed no abnormality. The hip joints were normal. During the period of hospitalization she received metacortelone orally and was discharged in January 1959. In April 1959 a laminectomy was done for a herniated intervertebral disk at L3–L4 and hip and shoulder roentgenograms at this time were normal. Because of recurrent thromobocytopenia purpura, decadron was administered from June 1959 until March 1960. Increasing hip and right shoulder pain developed and the patient was again hospitalized in August 1961 and roentgenographic examination at this time revealed bilateral avascular necrosis of the hips and shoulders.

Bone changes such as osteoporosis, joint narrowing, spur formation and subluxation may occur in patients under treatment for rheumatic or hypertrophic arthritis following systemic or intra-articular use of corticosteroids. These substances may produce bone changes similar to those of Cushing's disease of natural origin but no instance of aseptic necrosis has been reported in iatrogenic Cushing's syndrome, except in patients receiving treatment for arthritis. The glucocorticoids have several known effects on the skeleton including anti-anabolic, antitoxic and anti-inflammatory. However, the etiology of the bone and joint changes following steroid therapy is unknown. The two current theories as to the cause include overuse following pain suppression and local vasculitis secondary to increased viscosity and hypercoagubility of the blood.

The roentgen findings in the case reported were those of avascular necrosis of bone and the appearance was indistinguishable from avascular necrosis due to other causes. The time-dose relationship of steroid therapy sufficient to cause these bone changes is unknown but may appear as early as 3 months after the institution of therapy. Since these substances are in common use the authors feel that it is important that radiologists and other physicians be aware of this possibility.—*Edward B. Best, M.D.*

GIMES, B. Zur Differentialdiagnose entzündlicher Veränderungen im Ileosakralgelenk. (The differential diagnosis of inflammatory changes in the sacroiliac joint.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, May, 1963, *98*, 570–577. (Address: Röntgenklinik, Üllöi út 78/b, Budapest, VIII, Hungary.)

Pain in the sacroiliac joint may be due to a posttraumatic or an inflammatory condition. A tear in the posterior sacroiliac ligament may occur after repeated minor injuries or a more severe trauma and the pain may be caused by a localized hematoma, which may be missed on roentgenographic study in the early stages. In some cases, a hazy appearance of the articular surface may simulate a tuberculous or a rheumatoid arthritis, especially when no history of trauma is elicited. Follow-up studies in 4 patients with painful sacroiliac joints showed an osseous condensation on the iliac side of the joint. The author believes that this is due to alteration within the stripe-like apophysis frequently seen during puberty adjacent to the inferior angle of the sacroiliac joint. Interference with the blood supply of the apophysis produces an increased osteoblastic activity, which is recognized later as osseous condensation or osteitis condensans ilii.

The pathogenesis is considered to be identical with that of osteochondrosis or osteochondritis of many other bones.

The differential diagnosis frequently depends on their reaction to specific therapy.—*J. Zausner, M.D.*

TWIGG, HOMER L., and SMITH, BERNARD F. Jaccoud's arthritis. *Radiology*, March, 1963, *80*, 417–421. (Address: Georgetown University Hospital, 3800 Reservoir Road, N. W., Washington 7, D. C.)

Jaccoud's arthritis is a deforming condition involving the hands, and is sometimes seen after repeated attacks of rheumatic fever. It is characterized by ulnar deviation and flexion deformity of the metacarpal phalangeal joints with subluxation. The deformity in this disease appears to be due to a periarticular fascial and tendon fibrosis rather than to a synovitis as seen in true rheumatoid arthritis. There is associated periarticular soft tissue swelling. Usually the joint disease is inactive with little symptomatology and the joint function is maintained.

Initially the roentgenographic examination shows no bone involvement despite a faradvanced clinical picture. Only soft tissue swelling, and ulnar deviation of the metacarpal phalangeal joints may be demonstrated. Often the ulnar deviation is not apparent on the roentgenograms because it is voluntarily corrected by the patient. The earliest bone changes which can be seen are erosion of the metacarpal heads of the palmar and radial aspects producing a hook-like deformity. Rheumatoid arthritis will also show these findings but, in addition, there are more marked changes in the carpal bones and the articular surfaces of the interphalangeal joints.

Since the condition, to the knowledge of the authors, has not been reported in the radiologic literature, this report is presented in the hopes that it will enable radiologists to recognize it and suggest the diagnosis.

Two case reports are given.—*Donald N. Dysart, M.D.*

Babicky, Arnost, and Kolär, Jaromir. S^{35}-Stoffwechsel in bestrahlten wachsenden Knochen. (Sulfur 35 metabolism in irradiated, growing bones.) *Strahlentherapie*, Feb., 1963, *120*, 300–307. (Address: Dr. J. Kolär, Radiologische Klinik, U nemocnice 2, Prag 2, CSSR.)

Sulfur is taken up by the organic portion of bone. Less sulfur 35 is taken up by irradiated bone than by normal bone and even unirradiated bone in the irradiated animals has a similar depression of uptake. This speaks for some sort of general skeletal metabolic stimulus arising from local irradiation of bone.

The metabolic action of the organic component of bone precedes that of the inorganic component (as determined by calcium 45 studies). Thus, the radiation changes in bone must be basically the result of damage to the cells and organic matrix.—*Henry G. Moehring, M.D.*

Pappas, Arthur M., and Cohen, Jonathan. The abscopal effect of x-irradiation on bone growth in rats. *J. Bone & Joint Surg.*, June, 1963, *45-A*, 765–772. (From: Departments of Orthopedic Surgery and Pathology and Division of Laboratories and Research, Children's Hospital Medical Center and Harvard Medical School, Boston, Mass.)

This is a report from the Orthopedic Research Department of Harvard Medical School. The local and abscopal effects of irradiation to the extremities of rats were studied.

Using orthovoltage with a half value layer of 1.7 mm. Cu, comparable groups of rats were irradiated and then studied for 72 days. One group received 800 r to one knee (3 per cent of body volume), another 400 r, and a third 800 r to one hind extremity (10 per cent of body volume).

After 21 days all irradiated rats showed a significantly decreased weight as compared to the control group and retardation of growth in the irradiated tibiae. Only in the group receiving 800 r to one hind extremity were abscopal effects noted; specifically, significant retardation of growth in the unirradiated tibiae, ulnae, vertebrae and body length.

The abscopal effect appears to be associated with the volume of tissue irradiated as well as the dose.—*Martha Mottram, M.D.*

Schmidt, Benjamin José, Beçak, Willy, Beçak, Maria Luiza, Soibelman, Isaac, Queiroz, Antonio da Silva, Lorga, Antonio Paulo, Secaf, Feres, Antonio, Clemente Filho, and Carvalho, Azarias de Andrade. Metaphyseal dysostosis: review of literature; study of a case with cytogenetic analysis. *J. Pediat.*, July, 1963, *63*, 106–112. (Address: Clinica Pediatrica da Escola Paulista de Medicina, R. Napoleao de Barros, 761 São Paulo, Brazil.)

A case of metaphyseal dysostosis is described and added to the 37 cases already reported in the literature.

Physical examination. The patient is a 12 year old Brazilian male who had a growth arrest of 6 years' duration with gradual bending of his legs for the past 4 years. He was underdeveloped physically. Prognathism and pallor were present. The mouth was partly opened and the incisors protruded and were exaggerated in size. The neck was short and the chest cavernous, with pronounced depressions in the mammary region of both sides. There was dextroconvex scoliosis and dorsolumbar kyphosis. The intelligence quotient was 80 (Merrill's test).

Roentgen findings. The only positive finding in the skull was inclination of the floor of the anterior fossa. There was dorsolumbar kyphosis of the spine with generalized osteoporosis and spina bifida of L 4, L 5 and the sacrum. There was dorsal platyspondylia. The lumbar vertebral bodies were deformed with anterior protuberance of the median portions of the body. The region of the acetabulum in a hypoplastic pelvis showed a blown-out porous aspect with retardation of ossification. Marked coxa vara was present showing changes in the texture of the femoral metaphyseal zone, and there was pronounced genu valgum. Metaphyseal deformities with increase in volume, and alterations in texture and contour of the bones were evident. The upper extremities also showed metaphyseal deformities with alteration in texture and contour of the bones. The hands had a normal appearance.

Laboratory findings. These were not remarkable

Genetic studies. Karyotypic analysis of 97 cells showed 88 cells with 46 and 9 cells with 47 chromosomes. The 46 chromosome cells were apparently normal. The 47 chromosome cells presented an additional chromosome identified in all cells as chromosome 16.

Histologic examination. Microscopic study of a biopsy specimen revealed the general structures to be normal and in the medullary space there was connective tissue proliferation, showing the presence of osteoid tissue surrounded by osteoblasts.

Diagnosis. The diagnosis was based on the general appearance plus the roentgenologic findings. The clinical and laboratory data help exclude other conditions which enter the differential diagnosis. The karyotypic analysis in this one case does not allow correlation of the clinical findings with the alterations found.

Treatment. Administration of vitamin D produced no detectable improvement and a corrective osteotomy was performed.—*David Morse, M.D.*

REILLY, B. J., and MUNN, J. D. Metaphyseal dysostosis. *J. Canad. A. Radiologists*, June, 1963, *14*, 84–94. (From: Hospital for Sick Children, Toronto, Ontario, Canada.)

The severe form of metaphyseal dysostosis was first described three decades ago by Janzen. There is a derangement of metaphyseal ossification involving all long bones. Normal bone is replaced by irregular masses of calcified epiphyseal cartilage. Growth is stunted and varus and valgus deformities are produced. The hands are severely affected.

More recently, Schmid described a milder form of this disorder which is also assumed to be of genetic origin. The authors discuss 9 new cases of the Schmid form which were discovered in children aged 14 months to 11 years. These patients showed involvement of the long bones, but, unlike the severe form, the hands were unaffected; the victims were short and had bowed legs, but were otherwise normal.

The roentgenographic features in the milder form of the disorder consist of an irregular widening of the epiphyseal line in all the long bones. There is irregular cartilaginous proliferation in the metaphyses of the femoral necks, about the knees, ankles, shoulders, elbows, wrists, and similar changes cause cupping or beading of the ribs at the costochondral junction. Weight bearing produces coxa vara and genu valgum. Elswehere, bony texture is normal and the spine and skull are not involved.

Certain other entities mimic the changes of metaphyseal dysostosis, but they can usually be distinguished by the roentgenographic or biochemical features. Serum calcium and phosphorus are normal; the alkaline phosphatase may be slightly elevated. Rachitic osteodystrophies, particularly vitamin D refractory rickets, simulate metaphyseal dysostosis, but they can usually be distinguished by the diffuse coarsening of trabecular pattern throughout the skeleton. However, at least 3 patients presumed to have metaphyseal dysostosis have been successfully treated with large doses of vitamin D. The authors find these reports "surprising but stimulating." Precise diagnostic criteria which may serve to differentiate metaphyseal dysostosis from vitamin D refractory rickets are not presently available.

Hypophosphatasia resembles metaphyseal dysostosis roentgenographically; both disorders produce metaphyseal irregularities which may be strikingly similar. Fortunately, the alkaline phosphatase level is extremely low in hypophosphatasia and this test permits easy differentiation.

Other disorders may intrude in the differential diagnosis, but they usually demonstrate features which are distinctive and fundamentally different from the changes seen in metaphyseal dysostosis. Morquio's disease causes abnormality of the articular cartilage. Flattening of the ossification centers is seen in the epiphyseal dysplasias. There is a primary growth failure of the cartilaginous plate in achondroplasia. Cleidocranial dysostosis may produce individual lesions similar to those seen in metaphyseal dysostosis, but the sum of the clinical and roentgenologic signs serves to identify the two diseases.

The condition has been detected as early as 14 months of age. Prompt diagnosis is desirable so that the parents may be prepared to anticipate corrective orthopedic procedures. The disorder should be considered in patients with short stature and bowing of the legs, a peculiarity in gait or a limp and the diagnosis is supported by the detection of a widespread disorder of metaphyseal growth in a skeleton which is otherwise normal, without evidence of other systemic disorders or abnormality in serum calcium or phosphorus.—*Jack Reynolds, M.D.*

GORLIN, ROBERT J., MESKIN, LAWRENCE H., and ST. GEME, JOSEPH W. Oculodentodigital dysplasia. *J. Pediat.*, July, 1963, *63*, 69–75. (From: Division of Oral Pathology and Department of Pediatrics, University of Minnesota, Minneapolis, Minn.)

A new syndrome is described based on the authors' presented case and 6 cases previously reported in the literature.

The features are as follows:

Facies. The eyes are small and sunken. Ocular hypotelorism and a thin nose without alar flare produce a characteristic appearance.

Eyes. The eye anomalies are microphthalmia, iris changes and possibly glaucoma.

Extremities. The most common constant finding is camptodactyly of the fifth finger which is radially deviated. Clinically it appears to be shortened and on roentgenographic examination the middle phalanx is cube shaped. Hypoplasia of the middle phalanx of the fifth finger is seen in 60 per cent of mongols, 10 per cent of cretins and 1 per cent of normal individuals. Syndactyly of the fourth and fifth fingers is an occasional finding. The feet, ostensibly normal, roentgenographically demonstrate aplasia or hypoplasia of the middle phalanx of one or more toes. Hip dislocation and delayed ossification of the femoral heads have been described.

Hair. Dry, lustreless hair which fails to grow to normal length has been described.

Oral manifestations. Generalized enamel hypoplasia with resultant yellowish appearance of the teeth from the visible dentine is present. The alveolar ridge of the mandible is wider than normal.—*David Morse, M.D.*

Rask, Michael R. Morquio-Brailsford osteochondrodystrophy and osteogenesis imperfecta: report of a patient with both conditions. *J. Bone & Joint Surg.*, April, 1963, *45-A*, 561–570. (From: The Shriners' Hospital, Portland, Ore.)

The author reports the occurence of two separate inherited skeletal diseases in an 11 year old girl. The father had osteochondrodystrophy of the Morquio-Brailsford type and the mother osteogenesis imperfecta.

Numerous photographs and reproductions of roentgenograms are included of the parents as well as of the case reported.

It is postulated that both osteogenesis imperfecta and osteochondrodystrophy were inherited as dominant traits in this patient.—*David C. Alftine, M.D.*

Trias, Antoni, and Ray, Robert D. Juvenile osteochondritis of the radial head: report of a bilateral case. *J. Bone & Joint Surg.*, April, 1963, *45-A*, 576–582. (From: Department of Orthopaedic Surgery, University of Illinois, Research and Educational Hospitals, and the Presbyterian-St. Luke's Hospital, Chicago, Ill.)

Bilateral juvenile osteochondritis has been reported in the medical literature in only 6 previous cases.

The authors present the case of a white boy who was first seen at the age of 7½ years because of osteochondritis of the left femoral capital epiphysis. Four years later he was again seen because of pain in the left elbow. This was accompanied by considerable soft tissue swelling and warmth of the part involved. Subsequent roentgenograms demonstrated osteochondritis of both radial epiphyses.

The authors also give a review of the literature and bring out the fact that osteochondritis of the radial head is frequently associated with other skeletal diseases such as Osgood-Schlatter's disease. In their case there was an association with Leg-Calvé-Perthes disease.—*David C. Alftine, M.D.*

Burko, Henry, Watson, Janet, and Robinson, Margaret. Unusual bone changes in sickle-cell disease in childhood. *Radiology*, June, 1963, *80*, 957–962. (From: Departments of Radiology and Pediatrics of the State University of New York Downstate Medical Center and the Kings County Hospital Center, Brooklyn, N. Y.)

In general, three types of bony abnormalities occur in sickle-cell anemia: those due to marrow hyperplasia; those due to infarction; and those due to osteomyelitis, particularly *Salmonella* osteomyelitis. It is with the second of these, infarction, that this report is primarily concerned.

A review of the roentgenograms of 126 children with sickle-cell disease seen over a five-year period (1956–1961) at Kings County Hospital Center disclosed several unusual skeletal changes due to infarction. In 21 children, nearly all under the age of 2 years, painful swelling of the hands or feet, or both, known as the hand-foot syndrome, occurred. This is caused by infarction of the short tubular bones of the hands and feet. The bony changes are related to absorption of infarcted areas and hyperemic stimulation of adjacent periosteum causing subperiosteal new bone formation.

Infarction of an entire long tubular bone is an unusual occurrence in childhood sickle-cell disease, although localized infarction of a long bone is common. Infarction of an entire fibula was seen in 1 case. Bilateral symmetric scapular infarcts, which have not been previously reported, were seen in 2 children, resulting in subperiosteal new bone formation. The only instance in this series of associated *Salmonella* infection was a *Salmonella* chondritis of the sternum in a 4 year old child.—*Ralph Bowman, M.D.*

Cochran, W., Connolly, J. H., and Thompson, I. D. Bone involvement after vaccination against smallpox. *Brit. M. J.*, Aug. 3, 1963, *2*, 285–287. (Address: Dr. W. Cochran, Paediatric Surgeon, Ulster Hospital, Belfast, Ireland.)

Changes in bone after vaccination against smallpox are said to be very rare. The authors report a case confirmed by virus isolation.

The condition must be differentiated from other hyperostoses of infancy. The patient was vaccinated by scarification at age of 3½ weeks high over the deltoid and the reaction was severe, but subsided in 3 weeks. However, 28 days after vaccination, there was deepseated swelling over the scapula and roentgen study showed deposition of new bone on both surfaces of the body of the scapula. Biopsies of the scapula were taken on 3 different occasions and bacteriologic cultures were found to be sterile while inoculations on the chorio-allantoic membrane of embryonated eggs produced typical vaccinia virus pocks.

Seventy days after vaccination the child became ill with swelling of the lower jaw and subsequently periosteal bone proliferation involving the left body of the mandible was demonstrated. Two other episodes of illness occurred and were followed by the deposition of new periosteal bone on the ribs and then on the right side of the mandible. Slight destructive bone change was observed in the scapular region, but none was ever shown in the other areas of bone involvement. Progressive shrinking and remodelling of the scapula was observed.

The authors point out the striking similarity of certain features of this patient's findings with infantile cortical hyperostosis. The facies, the roentgen changes, and the microscopic picture simulate Caffey's disease.—*Richard E. Kinzer, M.D.*

Bendel, William L., Jr., and Race, George J. Urticaria pigmentosa with bone involvement. *J. Bone & Joint Surg.*, July, 1963, *45-A*, 1043–1056. (From: Department of Pathology, Baylor University Medical Center, Dallas, Tex.)

The case reported is added to the approximately 600 cases in the world's literature, and brings the number of cases that have been associated with infiltration of the bone or bone marrow by mast cells to 58. Urticaria pigmentosa is a chronic disease, principally of the skin, which begins usually in the first year of life, but may start shortly after puberty or in later adult life, affecting particularly males of light complexion. It is now recognized as a systemic disease, characterized by mast cell infiltration of the skin, bone marrow, lymph nodes, spleen, liver, and other organs which harbor the reticuloendothelial system. In fact some observers believe that this is a reticuloendothelial disease. The gross anatomic changes, such as lymphadenopathy, hepatosplenomegaly, bone lesions, etc., are produced by hyperplasia of the tissue mast cells and fibrosis.

The roentgenographic alterations in the bones consist of radiolucent zones which are bone resorptive defects produced by an underlying cellular hyperplasia, and areas of increased bone density which are the thickened trabeculae of the spongiosa and the thickening of the cortex of the long bones with narrowing of the marrow spaces. Those appearing as generalized osteosclerosis are caused by new bone formation.

The bone lesions have been found to be of two types, generalized and localized. In the generalized type is found cystic osteoporosis of the ribs with a thickening of the bone trabeculae, stippling of the bone structures in the skull, thickening of the skull tables, and generalized sclerosis of the pelvic bones and vertebrae. In the localized type are calcified deposits and decalcified areas of various sizes in the humerus, radius, femur, skull, and shoulder. Biopsy of these bones frequently reveals nodular, distinctly granulomatous lesions within the marrow spaces, with mast cells forming a large portion of the cellular constituents of these granulomas. Some investigations have, therefore, suggested that these lesions should be called mast cell granulomas of bone. Wide spread myelofibrosis, osteosclerosis, and pagetoid changes have been found associated with tissue mast cell accumulation in the marrow spaces.—*Donald M. Monson, M.D.*

Cruess, Richard L. The pathology of acute necrosis of cartilage in slipping of the capital femoral epiphysis: a report of two cases with pathological sections. *J. Bone & Joint Surg.*, July, 1963, *45-A*, 1013–1024. (From: New York Orthopaedic Hospital, Columbia-Presbyterian Medical Center, New York, N. Y.)

Three major complications of slipping of the capital femoral epiphysis may occur: acute necrosis of cartilage, aseptic necrosis, and later osteoarthritis. The last two sequelae are well recognized, but the first has scarcely been reported in the American literature.

This clinical entity consists of rapid destruction of the articular cartilage of both the femoral head and acetabulum after slipping of the capital femoral epiphysis. The changes are usually visible roentgenographically within a few months after the patient has sought medical attention for the epiphyseolysis. There is demineralization of the bone in the femoral head and about the acetabulum; the joint line rapidly becomes narrow and irregular. The femoral head usually shows no evidence of aseptic necrosis, although the two conditions apparently can occur simultaneously.

The symptoms caused by these pathologic changes are pain on motion of the hip and a limp. Severe muscle spasm about the hip and early flexion-adduction contracture develop.

The incidence of this particular complication in various series has ranged from approximately 1 to 15 per cent, without regard to method of treatment, but in some series the incidence was noted to be highest amongst Negroes. The occurrence of acute cartilage necrosis did appear, however, to be correlated with long time intervals elapsing before treatment, and with greater degrees of slipping. There was no clinical or laboratory evidence of an infectious or associated rheumatoid process, although the roentgenographic appearance frequently resembled a lowgrade inflammatory process such as tuberculosis which must be excluded.

Histologically, there is a nearly normal appearance of the bone structures in the presence of severe degenerative changes in the cartilage. Only the basilar layers of cartilage persist in many areas; there is virtually no synovial lining remaining and the capsular structures are greatly thickened. It is suggested that perhaps the most likely cause of death of the cartilage is interference with its nutrition as the result of extensive fibrosis of the synovial membrane and capsular structures coupled with adhesions between the synovial membrane and the femoral neck. Exactly why this should follow slipping of the capital femoral epiphysis remains undetermined.—*Donald M. Monson, M.D.*

Boyd, H. B., and Calandruccio, R. A. Further observations on the use of radioactive phosphorus (P^{32}) to determine the viability of the head of the femur: correlation of clinical and experimental data in 130 patients with fractures of the femoral neck. *J. Bone & Joint Surg.*, April, 1963, *45-A*, 445–460. (Address: 869 Madison Avenue, Memphis 3, Tenn.)

Even with modern techniques of internal fixation which have raised the rate of union of displaced fractures of the femoral neck to 85 per cent, there remains an incidence of avascular necrosis of portions of the weight-bearing aspect of the femoral head of 37 per cent in such patients. The authors assumed that necrosis develops because the blood supply of the head of the femur has been diminished as a result of the fracture, and sought a technique with which they could predict viability of the head fragment. The tracer used is P^{32}, apparently as inorganic phosphate, and it is administered to the patient at the rate of 2 μc/lb. of body weight. At the time of operation for the introduction of internal fixation devices, a guide pin is inserted through the lateral cortex of the greater trochanter, along the superior portion of the femoral neck, and entering the superior portion of the femoral head. The guide pin is withdrawn and a thin Geiger-Müller probe is inserted into the guide pin tract. With the aid of roentgenograms for localization of the counter, readings are taken within the substance of the trochanter, and within the superior portion of the femoral head. In an experience of 95 patients who had displaced femoral neck fractures, and who had been followed for 2 years or more to determine the accuracy of prediction of the isotope test, it was found that those patients in whom the ratio of counts within the trochanter to counts within the head was greater than 4.0 to 1 there was a greater likelihood of the development of avascular necrosis than in those patients in whom the trochanter/head count ratio was less than 4.0 to 1. A parallel group of 35 patients who had impacted fractures yielded results which seemed to bear out the validity of the trochanter/head count ratio.

The authors have had a sizable experience, and although they have not subjected their data to statistical analysis, it would seem likely that the test which they describe has a certain predictive value to the orthopedic surgeon who is attempting to assess viability of the head fragment.—*Frederick J. Bonte, M.D.*

Laurin, Carroll A., and Favreau, J. C. Rheumatoid disease in children. *Canad. M. A. J.*, Aug, 17, 1963, *89*, 288–301. (From: Department of Orthopedic Surgery, St. Justine Hospital, Montreal, Quebec, Canada.)

Juvenile rheumatoid arthritis should not be classified under the general heading of "Still's disease" since the latter name has been applied to those cases of rheumatoid arthritis in children which were associated with extensive visceral lesions and a bad prognosis. The case histories of 102 patients with juvenile or infantile rheumatoid arthritis seen between 1940 and 1960 were reviewed. Of the cases studied, only 45, or 44.1 per cent, could be finally shown to have a correct proven diagnosis. Among these 45 cases, 31 had adequate follow-up histories and this survey is based upon a careful analysis of these 31 patients.

The highest incidence of onset was in the first 2 years of life. There was a strong suggestion of hereditary background with a definite family history of arthritis or related diseases. The clinical picture was not characteristic but "fever of unknown origin" was a common first symptom. Rash was not uncommon. Joint symptoms were variable with 20 per cent of the patients having no joint symptoms at the onset. The first sign was articular in 80 per cent. Roentgenographic changes appeared late with osteoporosis usually occurring first. Laboratory help was disappointing.

Follow-up observations led the authors to conclude that the prognosis is not as unfavorable as formerly believed. Life expectancy is good and joint deformity is not necessarily too marked. The need for a more sensitive diagnostic test is noted.—*Richard E. Kinzer, M.D.*

Blood and Lymph System

Smith, Charles C., and Coe, Walter S. Dissecting aneurysm of the aorta: a review of 20 cases. *South. M. J.*, May, 1963, *56*, 461–464. (From: Department of Medicine, University of Louisville School of Medicine and the Louisville General Hospital, Louisville, Ky.)

Twenty cases of dissecting aneurysm of the thoracic aorta are reported and the presenting symptoms analyzed. It was the authors' opinion that if the symptoms of aneurysm in the chest are properly evaluated a few cases can be salvaged by surgery.

The differentiation between these conditions and myocardial infarction or cerebral thrombosis must be made to avert unwise use of anticoagulant therapy.

The 20 cases reported were found at autopsy and represented an incidence of 1 per 213 autopsies at the authors' hospital.

The pathology and locations of the lesion are discussed. The symptoms of these patients are also considered in detail: 4 of the last 7 patients exhibited hemiparesis upon admission; others presented initial symptoms of abdominal crisis; still others showed occlusion of the right subclavian artery. Most of the patients died within 2 hours of admission to the hospital; however, 7 survived 24 hours after admission. These lived long enough for a definitive diagnosis to be made and possible surgical intervention.

The surgical methods of dealing with the aneurysm are discussed.

The authors conclude as follows:

1. Patients with dissecting aneurysm may present themselves with widely diverse clinical manifestations; this diagnosis must be considered in every instance of chest pain, abdominal pain and cerebral infarction. Careful clinical observation will often reveal important clues to the correct diagnosis and perhaps allow surgical intervention.
2. The prompt recognition is essential to select candidates for surgical intervention without delay and to avoid errors in therapy, such as the administration of anticoagulants for a mistaken diagnosis of myocardial infarction or cerebral infarction.
3. The chest roentgenogram may be extremely valuable in corroborating the diagnosis in most cases involving the thoracic aorta.
4. The beneficial effect of creating "re-entry" is discussed in conjunction with Bernoulli's theorem.—*John H. Harris, M.D.*

Schmitz-Dräger, H. G. Zur Angiographie der Arteria subclavia. (Angiography of the subclavian artery.) *Fortschr a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, May, 1963, *98*, 521–542. (Address: Röntgeninstitut und Strahlenklinik der Städt. Krankenanstalten, Köln-Merheim, Germany.)

Arteriography provides the best means for the demonstration of the exact location and extent of involvement of the subclavian artery. Contrast visualization furnishes significant aid in the differential diagnosis of lesions in the superior mediastinum. It is especially used when vascular surgery is contemplated or to study the status of vascular grafts. The pathologic changes in the subclavian artery disclosed by this method may give valuable information concerning the condition of neighboring vessels, since alterations in these vessels are frequently similar, particularly in those arising from the aortic arch.

The choice of methods depends on: (1) the clinical findings regarding the site and type of the disease; (2) the ability to obtain maximum contrast at the required place; and (3) the avoidance of complications for the patient.

The available methods include: (1) exposure of the vessel and direct injection of the contrast material; (2) percutaneous injection; (3) catheterization to the desired site; (4) percutaneous retrograde aortography via the femoral artery; and (5) translumbar aortography. The latter method is used whenever generalized arterial spastic changes render angiocardiography inadvisable or inadequate.

The author prefers catheterization of the femoral artery because it produces relatively few and harmless side reactions; the degree of concentration of the contrast material is equal to that obtained by selective injection into the aortic arch or individual branches of the aorta. A contraindication is the inability to pass the catheter because of extensive involvement of the arteries of the pelvis or of the aorta, an aneurysm of the aorta at any level, and elongation and tortuosity of these vessels. This method is superior to a venous injection for visualization of the aortic arch, since it avoids the superimposition of contrast material in the large arm veins and it provides a greater amount of contrast material to this area. Catheterization via a brachial artery is performed in preference to angiocardiography when a stenosis of the aortic isthmus is suspected.

The diseases of the subclavian artery are classified as follows:

A. Congenital: 1. anomalies of origin; 2. alterations in connection with stenosis of the aortic isthmus and pseudocoarctation; and 3. congenital aneurysms and arteriovenous fistulas.
B. Acquired: 1. elongation and buckling; 2. aneurysms: traumatic, sclerotic, luetic, and those associated with anomaly of the thoracic inlet; 3. stenoses and strictures: traumatic, inflammatory, arteriosclerotic, and those secondary to anomalies of the thoracic inlet; and 4. arteriovenous fistulas.

The site of origin of the subclavian artery and its interrelationships with other vessels vary considerably. Two or more branches of the aorta may be so close as to have a common origin from the arch. The number of branches may be more or less than normal. Fewer branches are seen in association with a double aortic arch or a common bicarotico-subclavian trunk. An example of an increase is the isolated origin of each carotid artery. A fairly common anomaly is the crossed subclavian artery (arteria lusoria). Dilatation of the aorta and its main branches is frequently seen in cases with stenosis of the aortic isthmus. In this condition, the subclavian artery is usually dilated and the ribs are notched (more commonly on the right side). In pseudocoarctation, the left subclavian artery is dilated and arises more distally than its usual site of origin. Congenital aneurysms and fistulas of the subclavian artery are uncommon.

Buckling of the subclavian artery is probably due to degenerative changes and hypertension. The condition may be suspected in the presence of an asymptomatic swelling at the insertion of the sternocleidomastoid muscle and it may be responsible for a Horner's syndrome. Acquired aneurysms of the subclavian artery are rare. The diagnosis is important because of their tendency to rupture, their pressure on neighboring organs, and the possibility of stenosis. The symptoms include local pain, dyspnea, dysphagia, paresthesia in the arm and alterations of the pupil on the homolateral side. Aneurysms may be due to a cervical rib or an abnormal position of the anterior scalenus muscle. The effects of stenosis or stricture of the subclavian artery depend chiefly on the efficiency of the collateral circulation. Some patients may develop gangrene of the involved extremity and others may be asymptomatic. The subclavian artery may become involved as a result of a "whiplash" injury, direct trauma to the vessel or secondary to a fracture of the clavicle.—*J. Zausner, M.D.*

Gough, M. H., Guiney, E. J., and Kinmonth, J. B. Lymphangiography: new techniques and uses. *Brit. M. J.*, May 4, 1963, *1*, 1181–1184. (From: Department of Surgery, St. Thomas's Hospital Medical School, London, England.)

The authors devote a large section of their article to materials and techniques used in their work with lymphangiography. Of interest is the fact that they prefer general anesthesia in performing their studies and the use of a Zeiss operation microscope for dissection and injection of the contrast material. Diffusible dye patent blue violet is employed for identification of the lymphatics and ultrafluid lipiodol, which is similar to ethiodol, as the contrast agent. Dosage schedules used were 0.25 to 0.3 ml./kg.

Four case reports are presented with pertinent lymphangiograms of the pathologic conditions.

There follows a short discussion of endolymphatic radiation therapy that they have utilized. They now infuse radioactive gold into the appropriate lymph trunks (and thus into the regional lymph nodes) in all patients with malignant melanoma of the limb. This is done in the absence of clinical lymphadenopathy. Au^{198} doses for the leg have been from 50 to 70 mc, and in the arm from 30 to 40 mc. The doses are infused in a volume of 30 mc/ml. at a rate of about 0.4 ml./minute. Following treatment there may be a brisk local reaction at the lymph node sites, which subsides after 6 to 10 days, and leaves the lymph nodes somewhat enlarged and indurated. The authors state that the results in a small number of patients who have been followed for 3 years have been encouraging.—*William K. Littman, M.D.*

Wellauer, Josef, del Buono, M. S., and Rüttimann, A. Die Lymphographie als neues Ermittlungsverfahren des Metastasenstatus im TNM-System. (Lymphography as a new means of establishing the status of metastases in the TNM-system.) *Strahlentherapie*, April, 1963, *120*, 631–640. (From: Röntgendiagnostisches Zentralinstitut und Radiotherapeutische Klinik der Universität, Zürich, Switzerland.)

For more accurate classification, lymphography replaces palpation as a clinical means of establishing the status of metastases in the TNM classification system (T—primary tumor; N—lymph nodes; M—distant metastases), particularly in evaluating malignancies of the genitourinary tract and the rectum.—*Henry G. Moehring, M.D.*

RADIATION THERAPY

Hope-Stone, Harold F., Blandy, John P., and Dayan, Anthony D. Treatment of tumours of the testis; 282 testicular tumours seen at the London Hospital during 1926–61. *Brit. M. J.*, April 13, 1963, *1*, 984–989. (From: Departments of Radiotherapy, Urology, and Pathology, The London Hospital, London, England.)

The authors present an analysis and discussion of 201 testicular tumors treated by simple orchidectomy and postoperative irradiation between 1926 and 1961 at the London Hospital. One of the main reasons of the study was reappraisal of the value of lymphadenectomy in the treatment of testicular tumors, and in particular, teratomas. The multiple sources of error are considered in comparing results from different centers, especially as regards the pathologic classification. Quite a lengthy discussion about this problem is presented. As an example is cited the incidence of seminoma which is given as 35.4 per cent in a series of Patton *et al.* (1960), whereas in most British series it may amount to 50 to 60 per cent of the total.

In the present series of 201 cases suitable for analysis, simple orchidectomy was performed and when the wound healed, the patient was treated with irradiation. Since 1958 cobalt 60 teletherapy was employed to treat all cases, using a pair of parallel and opposing fields, treating pelvic and para-aortic lymph nodes as a unit to a tumor dose of 3,000 rads in 4 weeks for seminoma and 3,500 to 4,000 rads in 4 weeks for teratoma and embryonal carcinoma. The kidneys were shielded by lead blocks.

A chart depicts the age incidence and in this series shows that seminoma involves an older age group of men, whereas teratoma is essentially a disease of young men. This is at variance with some other reports.

In the whole series there were: 54.4 per cent seminoma, 42 per cent teratoma, and 3.6 per cent other tumors according to Dixon and Moore (1952); compared to the classification of Patton *et al.* (1960), the latter give a much lesser incidence of seminoma and much greater incidence of embryonal carcinoma.

The clinical features as to modes of appearance of the tumors and incidence in undescended testes are described.

The present analysis revealed an 87 per cent crude survival rate for seminoma and 68.7 per cent for teratocarcinomas. The 68.7 per cent is compared with Patton's (1960 and 1962) results of 54.5 per cent crude survival rate for teratocarcinomas. The authors suggest that their seminoma group may have some tumors that would have been classified as embryonal carcinoma in Patton's group which would have the effect of excluding a substantial proportion of less malignant tumors from their series.

The authors conclude that the results with radiation therapy are not only not significantly worse but may even be a little better than when lymphadenectomy is added, and this prompts a more critical appraisal of the theoretic basis on which lymphadenectomy has been advocated. Also, the assumption that certain teratomas are radioresistant is discussed and the view is expressed that this assumption is open to criticism. They state that present day evidence supports the fact that proper treatment for all varieties of testicular neoplasm is orchidectomy, supplemented by radiation therapy, without surgical removal of the abdominal lymph nodes.—*William K. Littman, M.D.*

Flocks, R. H. Combination therapy for localized prostatic cancer. *J. Urol.*, June, 1963, *89*, 889–894. (From: Department of Urology, University of Iowa, Iowa City, Iowa.)

The author presents a classification of the stages of prostatic cancer which is clinically useful. He divides this disease into local lesions limited to the prostate, with subdivisions of lymph node and bone marrow dissemination; and local lesions with extraprostatic invasion which includes approximately 80 to 95 per cent of his cases. Similarly, the latter group is divided into those who have lymph node or bone marrow dissemination and those who do not exhibit such dissemination.

Patients with carcinoma confined within the capsule of the gland have a good prognosis following radical surgery. In those instances, where the disease has extended beyond the prostatic capsule, evaluation is made by lymph node biopsy and bone marrow evaluation. Some of these early cases can be treated by radical prostatectomy combined with radioactive gold instillation as adjuvant therapy. This combination has been used in a total of 41 patients with excellent results in that only 2 developed local recurrence. These 2 patients were from a group with large local lesions and much local extension. Four of 32 cases followed over 10 years and 7 of 12 cases followed 8 years are alive and clinically free of cancer after such therapy. Other forms of adjuvant therapy such as cobalt 60 teletherapy, alkylating agents, large doses of diethylstilbestrol, or endocrine management might also be very valuable in these situations. In some instances pulmonary metastases have disappeared following the use of nitrogen mustard intravenously and the same results may be seen after the administration of diethylstilbestrol.

There are 8 simple and compound diagrams to illustrate this article.—*George W. Chamberlin, M.D.*

Moore, J. G., Chang, Norman H., Scott, Earl, and Morton, Daniel G. The early assessment of irradiation therapy in cervical cancer. *Am. J. Obst. & Gynec.*, July, 1963, *86*, 677–692. (From: Department of Obstetrics and Gynecology, UCLA School of Medicine, Los Angeles, Calif.)

In attempting to predict the effectiveness of radiation therapy in cervical cancer two other parameters are evaluated in addition to the conventional radiation response (RR). These are the initial radiation response (IRR) and the clinical response (CR). The aim is to obtain a reliable measure of radiocurability at a time early enough so that treatment failures could be identified and effective surgical intervention could be instituted.

The IRR index is determined in the same fashion as the RR with specimens being obtained at 7 and 10 days after completion of the first vaginal radium application. The CR index represents the clinical observations made during the first 6 weeks following radiation therapy and includes a general appraisal and evaluation of superficial healing of the lesion, chrinkage of the cervix and associated tumor tissue, disappearance of induration and the attainment of pliability of tissues and movability of pelvic structures.

A total of 111 patients was studied with histologic diagnoses and staging being utilized throughout. The radiation therapy schedule whenever possible was radium, external irradiation and radium over a 30 day period. The cytologic methods are described in detail. The patient survival follow up figures are given in terms of 1–5 years with 81 per cent of the patients being 2 years or more post-treatment.

Seventy-seven per cent of patients in whom a good RR response was seen were alive and well from 1 to 5 years after treatment. In Stage I and II 87 per cent of patients with a favorable RR were alive and 70 per cent of patients with a poor RR were dead during the observation period.

Evaluating the IRR and patient survival in Stage I and II cases, 83 per cent of the patients with a good IRR were alive and well and 33 per cent of the patients with a poor IRR were alive and well during the observation period—percentages quite similar to the RR correlation with patient survival.

Correlating patient survival with combined CR and cytologic response (CR+RR) in Stage I and II cases, a 92 per cent survival was noted when a good CR plus RR occurred and no patients with a poor CR and poor RR were alive.

The authors feel that the IRR is a valid cytologic test in the early assessment of radiation sensitivity but point out the fact that the series is small, the follow up period is short and the methods are complex.—*Philip Rubin, M.D.*

MILICEVIC, DRAGOSLAV, and NIKOLIC, SLOBODAN. Beobachtungen über die Ursachen des Auftretens von Armödemen bei behandelten Mammakarzinomen sowie Möglichkeiten ihrer Verhütung. (Observations of the causes, and their avoidance, of arm-edema in treated carcinomas of the breast.) *Strahlentherapie*, Feb., 1963, *120*, 219–227. (From: Chirurgische Abteilung des Instituts für Krebsforschung der Medizinischen Fakultät, Belgrad, Jugoslavia.)

The authors studied 370 patients with carcinoma of the breast during 1955–1960. Of 224 patients treated for mammary carcinoma during the first 3 years, 30.1 per cent developed edema of the arm (even slight edema detectable only by measuring the two arms was included). Of those not receiving preoperative irradiation (168 patients), 13 per cent developed edema, as compared to 64.6 per cent of the preoperatively irradiated (irradiation consisted of 1,000–2,000 r to each of these fields: axillary, parasternal, supra- and infraclavicular, and medial and lateral tangential mammary). Of the patients treated in 1960, 21.8 per cent developed arm edema (those not receiving preoperative irradiation, 11.1 per cent; and those with preoperative irradiation 35.7 per cent).

In contrast with this effect of preoperative irradiation, no relationship could be demonstrated between postoperative irradiation and arm edema. From the surgical standpoint, sparing the pectoralis minor muscle reduced the incidence of arm edema.

Phlebography demonstrated instances of stenosis of the axillary vein after preoperative irradiation, before operative treatment; therefore, irradiation is presumed to be the cause of this stenosis. In a number of patients, surgical re-intervention after development of edema showed massive, stricturing scar formation about the axillary vein. Excision of this scar tissue resulted in decrease of the edema if the excision was done within 3 months of the appearance of the edema.

The authors conclude that arm edema results from obliteration of the axillary vein and blockage of the lymph channels with failure of formation of collateral venous channels via the cephalic vein. Retention of the pectoralis minor muscle, particularly in patients irradiated preoperatively, considerably decreases the incidence of arm edema. They advocate early postoperative mobilization of the extremity and close attention to attaining primary wound healing.—*Henry C. Moehring, M.D.*

SEDLIN, ELIAS D., and FLEMING, JOSEPH L. Epidermoid carcinoma arising in chronic osteomyelitic foci. *J. Bone & Joint Surg.*, June, 1963, *45-A*, 827 838. (From: Henry Ford Hospital, Detroit, Mich.)

The authors note that 90 cases of epidermoid carcinoma arising in cases of chronic osteomyelitis have been reported in the literature since 1940 and they add 13 cases. Squamous cell carcinoma of the extremities comprises 1 to 2 per cent of all squamous cell cancer, and of these 2.5 to 4.5 per cent are secondary to osteomyelitis. The incidence of epidermoid carcinoma in chronic osteomyelitis is approximately 0.5 per cent.

In the reported cases there was a 30.5 year mean duration of the osteomyelitis before the development of carcinoma. It occured most frequently in middle aged men in the lower extremity and the malignant change developed in the epithelium lining the sinus. Sarcoma, adenocarcinoma, basal cell carcinoma and plasmacytoma have also been reported.

The symptoms caused by the carcinoma are usually manifested as an exacerbation of chronic or intermittent symptoms of a chronic osteomyelitis. There is pain, increased discharge, fetor and an ulcer or mass may develop at the mouth of the sinus or the lesion may be deep in the tract. Occasionally there may be bleeding or pathologic fracture. Associated with this there is often local inflammation and the enlarged lymph nodes may therefore be either inflammatory or metastatic.

Roentgenographic studies as a rule show no bone changes, but occasionally radiolucency may occur in a previous area of sclerosis or there may be a more pronounced zone of bone destruction.

In the cases collected from the literature metastases occurred within 18 months, and therefore a patient who survives 3 years can be given a good prognosis. Metastases can be expected to occur in 20 to 30 per cent of cases. In the 102 cases reviewed 22 had regional or visceral metastases and only 3 survived.

Amputation is usually the treatment of choice. The authors feel that enlarged regional lymph nodes should be biopsied when the primary lesion is biopsied. If these are positive, a radical lymph node dissection followed by irradiation should be done in addition to amputation.

The 13 cases are well documented and there are roentgenographic reproductions of 3 cases showing bone destruction due to tumor growth. References are given for all the 90 cases reported in the literature since 1940.—*Martha Mottram, M.D.*

ROSE, RAYMOND G., HARTFIELD, JAMES E., KELSEY, MAVIS P., and MACDONALD, ELEANOR J. The association of thyroid cancer and prior irradiation in infancy and childhood. *J. Nuclear Med.*, July, 1963, *4*, 249–258. (From: The Endocrine-Isotope Service, Department of Medicine, and the Department of Epidemiology, The University of Texas M. D. Anderson Hospital and Tumor Institute and The University of Texas Postgraduate School of Medicine, Houston, Tex.)

Of 426 cases of thyroid cancer seen at the M.D. Anderson Hospital from 1944 to 1961, a total of 216 living patients were followed up at the time of this report.

Seventy of the 216 had received prior irradiation with 63 of the 70 being irradiated in the head, neck and chest area. Acne of the face and neck was the most common cause for irradiation. Five cases received thymic irradiation. The average latent period from irradiation to diagnosis of thyroid cancer was 12 years.

One hundred and seventy five of the 216 patients were matched with respect to age, ethnic group and geographic residence as far as possible with 175 presumably well patients from the Strang Cancer Prevention Clinic in New York City. The latter acted as a control group.

Comparing the M.D. Anderson patients with the Strang patients there was a significantly higher incidence of cancer in the irradiated patients than in those with no previous irradiation. Caution is advised in the use of irradiation for benign head, neck and chest conditions in infants and children.—*Philip Rubin, M.D.*

FRISCHBIER, HANS-JOACHIM, and KUTTIG, HELMUT. Der Schutz der Augenlinse in der Telekobalttherapie. (Protection of the lens during telecobalt therapy.) *Strahlentherapie*, Jan., 1963, *120*, 119–122. (From Czerny-Krankenhaus für Strahlenbehandlung der Universität, Heidelberg, Germany.)

During telecobalt therapy of fields which include the eye, the authors protect the lens by inserting a 12 mm. lead cylinder, 8 cm. long in the beam. They describe the arrangement for attaching this cylinder to the radiation port and for shifting it, as required, in the beam; it may be placed eccentrically.

Isodose curves indicate that the dose at the lens is approximately 10 per cent of the maximum dose in the field.—*Henry H. Moehring, M.D.*

RADIOISOTOPES

RAZZAK, MUHAMMAD ABDEL. The use of a modified radioactive test for evaluating the peripheral circulation. *J. Nuclear Med.*, May, 1963, *4*, 244–248. (From: Faculty of Medicine, Cairo University, and Atomic Energy Establishment, Cairo, U.A.R.)

The peripheral circulation can be studied by using either nonradioactive or radioactive tests. The nonradioactive tests are indirect and have many variables that are difficult to control and to interpret, whereas tests using radioactive isotopes are direct and have fewer variables.

Radium C was used to study the peripheral circulation by Blumgart and Yens in 1927. Artificial radioactive isotopes were subsequently used, and there were problems in diffusibility and irregular distribution. Krieger developed an accurate method using radioactive iodinated human serum albumen (RISA) for evaluating the peripheral circulation. The author modified Krieger's method by lowering the dose of RISA and using tolazoline hydrochloride (priscol) instead of heat to dilate the vessels.

The modified tests were done in a quiet, draft-free and relatively constant temperature room. Twenty microcuries of RISA were injected and the uptake was measured by a scintillation detector placed in contact with the ball of the foot. The detector was attached to a counting rate meter and a strip chart recorder. When a plateau was reached, 10 mg. of priscol was injected and 3 minutes later another 20 μc of RISA was injected; the difference between the uptake curves obtained before and after the priscol injection was calculated as a percentage of the original uptake curve.

Forty-two cases were studied, and the increased radioactivity build up curve was 56±17 per cent (range 30 to 91 per cent) in normals, and 15±7 per cent (range 2 to 25 per cent) in those with poor peripheral circulation. The results obtained from the tests agreed well with the clinical findings.—*Charles W. Cooley, M.D.*

SODEE, D. BRUCE. Clinical usefulness of the I^{131} triiodothyronine erythrocyte uptake test. *J.A.M.A.*, July 13, 1963, *185*, 100–102. (Address: Walter Reed Army Medical Center, Washington, D. C.)

A total of 1,223 I^{131} *in vitro* triiodothyronine erythrocyte uptake tests was done on 1,033 patients using the method of Hamolsky, Stein and Freidberg.

Euthyroid patients (667) showed an 85 per cent correlation with the clinical impression of euthyroid state with 115 patients showing an elevated value for reasons unknown and 2 patients showing low values.

Hyperthyroid patients showed a 98 per cent correlation with the clinical hyperthyroid state. Following I^{131} therapy a few patients showed elevated erythrocyte uptake values even though their clinical states had returned to normal.

Hypothyroid patients of pituitary origin showed 82 per cent correlation and surgically induced or I^{131} induced hypothyroidism showed a 60 per cent correlation with the clinical hypothyroid state. The PBI and RAI uptake values showed 95–100 per cent correlation in these two groups.

A list of factors which increase, decrease or have no influence on the erythrocyte uptake test is given and sources of technical errors in performing the test are enumerated.

The author concludes that the *in vitro* erythrocyte uptake determination is a useful supportive test in the evaluation of thyroid function, particularly when iodine medication or roentgenographic contrast media interfere with the I^{131} uptake and PBI determinations.—*Philip Rubin, M.D.*

Toro-Goyco, E., Ramirez, Eli A., and Rivera, Julio V. The binding of radioactive triiodothyronine by erythrocytes in myocardial infarction. *Am. J. M. Sc.*, June, 1963, *245*, 692–698. (From: Radioisotope and Medical Services, Veterans Administration Hospital and the Departments of Medicine and Biochemistry and Nutrition, School of Medicine and School of Tropical Medicine, University of Puerto Rico, San Juan, Puerto Rico.)

Thirty-three cases of acute myocardial infarction were studied, especially regarding the erythrocyte uptake of radioactive triiodothyronine (T_3). Serial determinations were made in 24 of the cases. A transient elevation of the T_3 uptake was found in 19 cases. The elevation usually appeared during the first week and the peak values were between 20 and 25 per cent (normal 11.5 to 18.5 per cent). The abnormal level persisted from 2 to 5 days. The administration of heparin and dicumarol did not influence the T_3 uptake values.

Twenty-two cases with various types of cardiac arrhythmias were also studied regarding the erythrocyte uptake of T_3, and 7 cases showed elevated values. These 7 cases had either myocardial infarction, advanced liver or renal disease.

The authors suggest that possibly some unknown substance or substances could be released from the damaged myocardium that would increase the affinity of the erythrocytes for T_3.—*Charles W. Cooley, M.D.*

Ackerman, Norman B., and McFee, Arthur S. Radioisotope liver scanning in children as a diagnostic aid to the surgeon. *Surg., Gynec. & Obst.*, July, 1963, *117*, 41–43. (From: Department of Surgery, University of Minnesota Medical School, Minneapolis, Minn.)

The authors have performed radioisotope scanning of the liver on children of all ages, from 3 months upward without any untoward reactions. It is often necessary to administer moderate sedation to younger patients since they must remain still during the procedure which lasts for 20 minutes to 1 hour depending upon the liver size.

The method has been found helpful in the diagnosis of space-occupying lesions of the liver, the differential diagnosis of abdominal masses, the determination of position and size of the liver, evaluation of the results of chemotherapy and radiation therapy, and preoperative evaluation of patients with malignant tumors.

Several representative scans are presented which vividly demonstrate the usefulness of the procedure. —*Francis P. Shea, M.D.*

Zuppinger, A., Poretti, G., Schwarz, K., Zaoralek, P., and Aebi, H. Disturbances in the tritium content in organs after irradiation. *Radiol. clin.*, 1963, *32*, 402–410. (Address: Prof. Dr. A. Zuppinger, Röntgeninstitut der Universität, Inselspital, Bern, Switzerland.)

The tritium content of the organs of mice subjected to x-irradiation (250 kv., half value layer of 1.2 mm. Cu, filter 0.5 mm. Cu) was determined after the instillation of tritiated water (THO) intraperitoneally. There were changes in the tritium content of the tissues at different times after irradiation. There was a biphasic course of the tritium content in the brain and liver during the first 2 weeks after irradiation and this was thought to be due to a greater disturbance in the elimination of THO than in the uptake of THO. The depression of the tritium content 2 weeks after irradiation was thought to be due to a greater disturbance in the uptake of THO.

The tritium content in the skin of rats subjected to x-irradiation (100 kv., half value layer of 1.78 mm. Al, 2,000 r in one seance) was determined after the injection of THO intraperitoneally. The results were similar to those found in the mice studies. There was also an indirect radiation effect in the nonirradiated skin of a locally irradiated rat. The nonirradiated leg showed an equal disturbance in the tritium uptake as compared to the symmetric irradiated leg.

The authors reported the above (although incomplete) results, as they felt that this method of study could give valuable information regarding the mechanism of action of ionizing radiation. The indirect effect can explain certain general reactions after a clinical treatment and can lead to a better understanding of the nature of radiation damages.—*Charles W. Cooley, M.D.*

Allt, W. E. C., and Hunt, J. W. Experience with radioactive tantalum wire as a source for interstitial therapy. *Radiology*, April, 1963, *80*, 581–587. (Address: The Princess Margaret Hospital, 500 Sherbourne Street, Toronto 5, Ontario, Canada.)

Since January 1959, 126 cases of cancer of the mouth and neck have been treated using tantalum 182 wire, and 73 of these have been followed for one or more years. Ta^{182} has a half life of 111 days, with 90 per cent of its energy in the approximate 1.2 mev. gamma range. The K factor is 6.1 r/hr./mc at 1 cm., as against 8.25 r/hr./mc at 1 cm. for radium. There is little difference between characteristics of the radiation from radium, Co^{60}, or Ta^{182}. The Ta^{182} is supplied in two strengths, with cross section diameters of 0.2 mm. and 0.28 mm., and linear strengths of 0.4 and 0.7 mg. radium equivalent per centimeter of wire. The wire is surrounded by a 1 mm. sheath of platinum and is not appreciably absorbed from tissue implants.

The wire is highly malleable and ductile, being easily cut to the correct length and may be bent to any desired shape. This is of advantage in use about the mouth and neck, giving good isodose patterns and being more comfortable for the patient. The basic technique has been after-loading, using spinal needles, then securing the wire with small split shot. Used wire is returned to the Atomic Energy Commission of Canada for disposal. Use of Ta^{182} wire requires a good Physics Department for measurement and calibration.—*James C. Moore, M.D.*

MISCELLANEOUS

TORI, G., and GASBARRINI, G. Alterations of the microscopic structures of the human intestinal mucosa irradiated by means of small doses of x-rays. *Radiol. clin.*, 1963, *32*, 47–56. (Address: Prof. Dr. G. Tori, Radiological Institute, and Dr. G. Gasbarrini, Institute of Clinical Medicine of the University, Bologna, Italy.)

Gross and microscopic alterations of the small intestine are well known following large doses of radiation, and usually the larger the dose, the more serious the changes. Most experimental studies have been done using large doses of radiation.

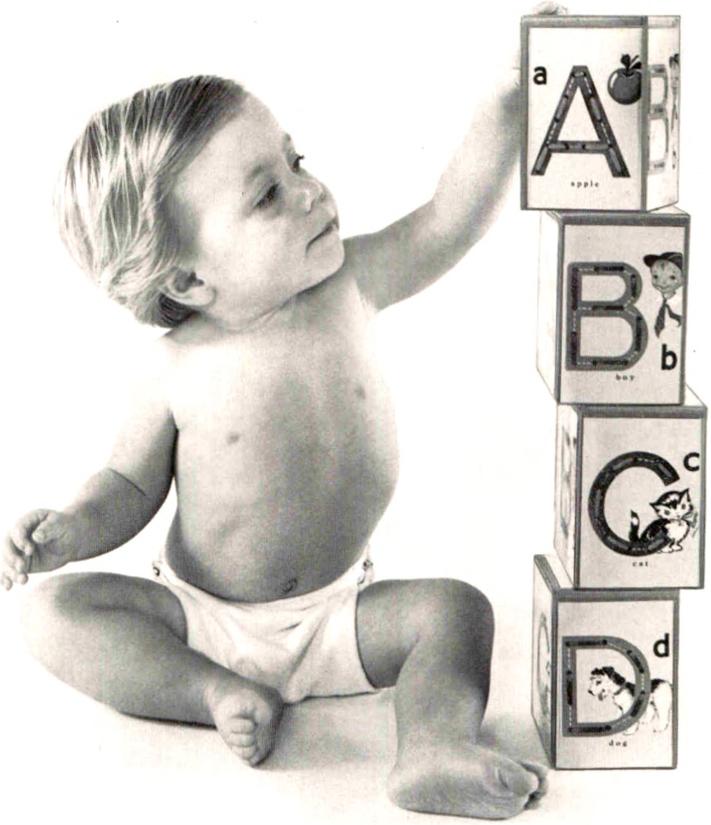
The purpose of the present study was to determine the changes in the small intestine by means of the electronic microscope after administration of radiation doses of 50 and 100 rads through a 8 × 10 cm. field in 10 patients undergoing treatment for carcinoma of the uterine cervix.

Biopsy of tissue was obtained *in vivo* and immediately fixed for microscopic study. Reported observations concern only the epithelial cells lining the villi. There were two groups of 5 patients, one group having received 50 rads and the other 100 rads. Tissue was obtained 4, 6, and 12 hours following irradiation. In the patients receiving 50 rads, no change was seen. There were changes in the patients who received 100 rads; these changes involved the ultrastructures and consisted of the presence of large-sized endocytoplasmatic granules and alterations of the microvilli.

The authors submit the hypothesis that the granular formations may represent different metabolic conditions in the structures which make up the enzymic patrimony of the cells.—*William K. Littman, M.D.*

SCHINZ, H. R., and WIDERÖE, R. (Zürich, Switzerland.) Das Planck und das rad: Probleme der Strahlenmessung in neuer Sicht. (The planck and the rad: problems in radiation measurements from a new point of view.) *Schweiz. med. Wchnschr.*, June, 1963, *93*, 837–838.

The authors again call attention to the lack of clarity in the present-day conception of definitions and units in the fields of measurement of radiation energies (radiometry) and radiation dosages (dosimetry). They feel that a clear uniformity in these measurements is only possible if definite practical units are made available for these two areas. In order to accomplish this they propose a new special unit—the *planck* (p) 3,000 erg/cm².—for the measurement of the density of radiation in a field of quanta of particle radiation. The unit of radiation intensity (1 p/sec. or 3,000 erg/cm². × sec.) together with the *rad* (100 erg/gram), the unit for absorbed dose, covers practically all radiologic measurements. The *roentgen* is based on measurement of ionization in air. It should be regarded as a supplementary unit for special measurements and as an intermediate step in the evaluation of radiation densities in *plancks* and dosages in *rads*.—*Otto Glasser, Ph.D.*



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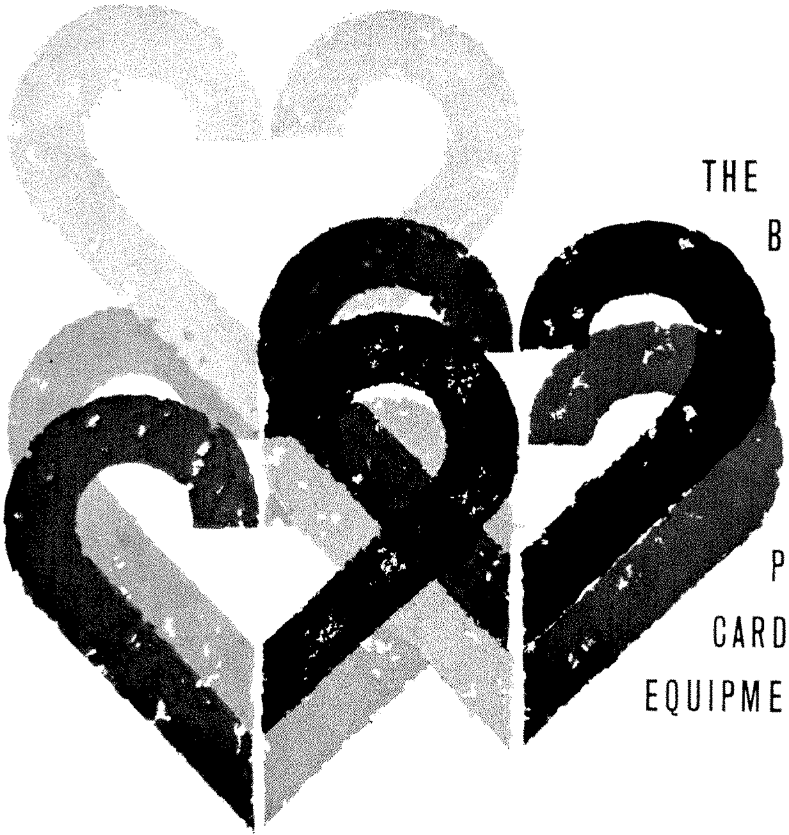

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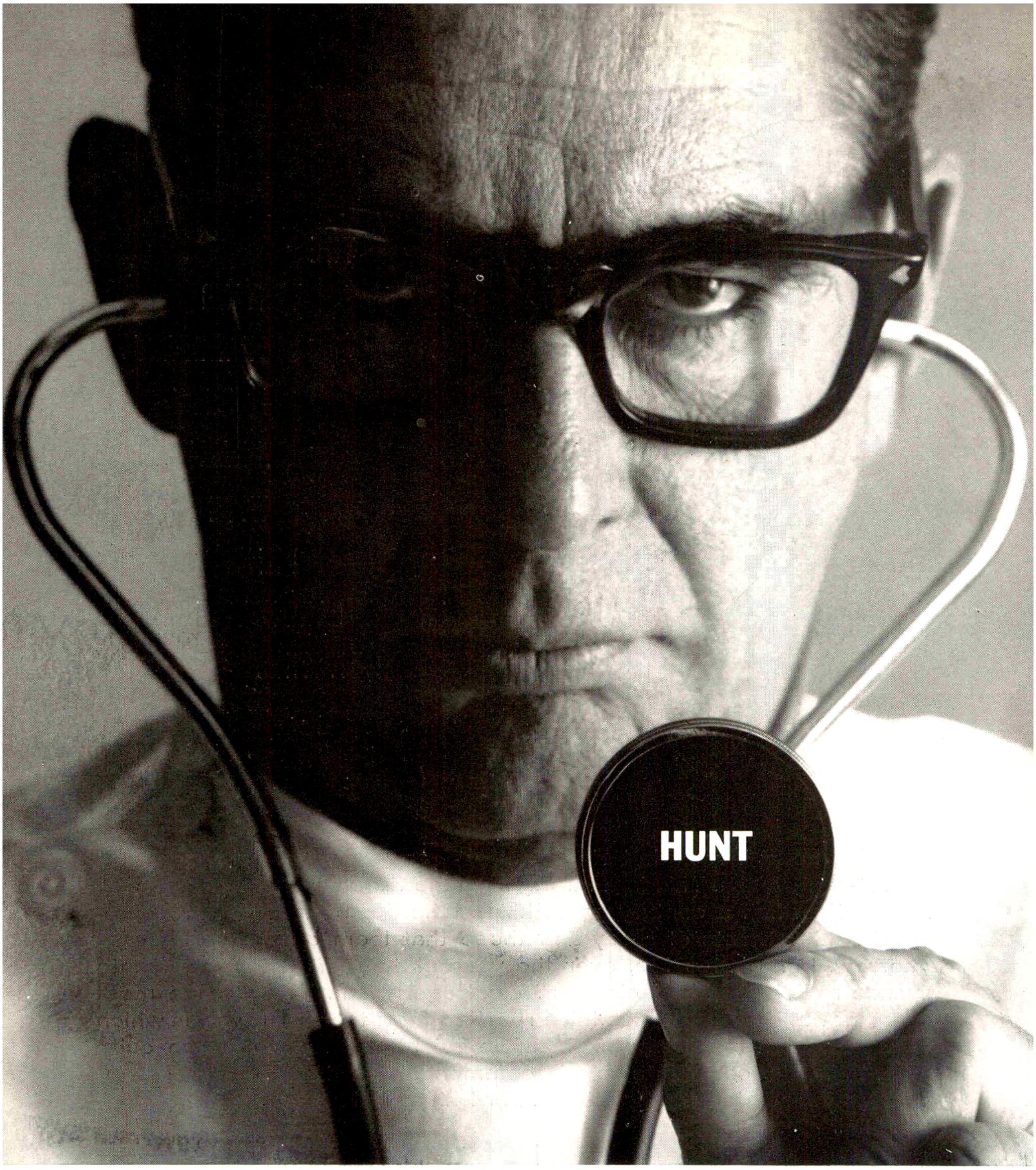

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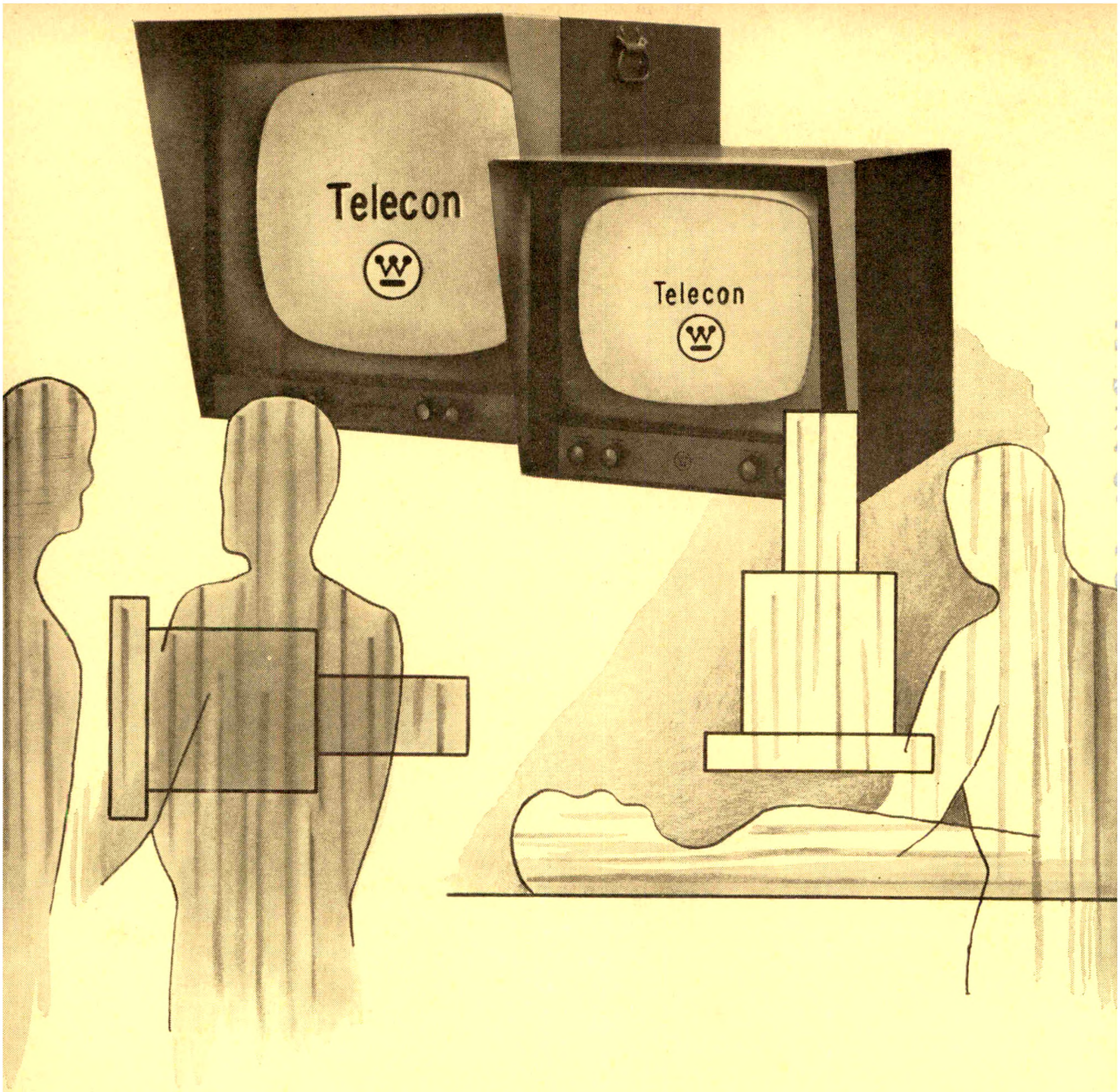

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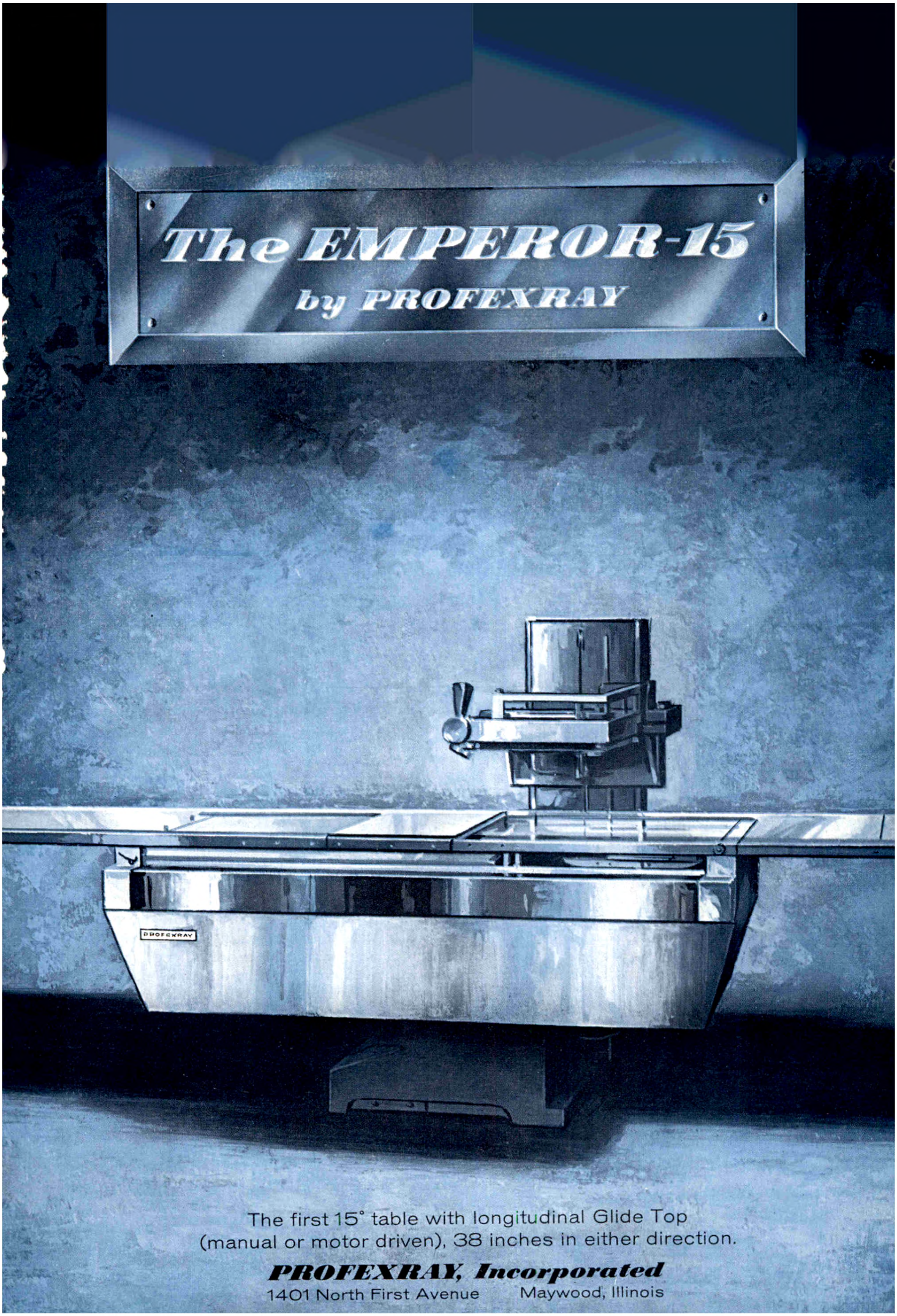

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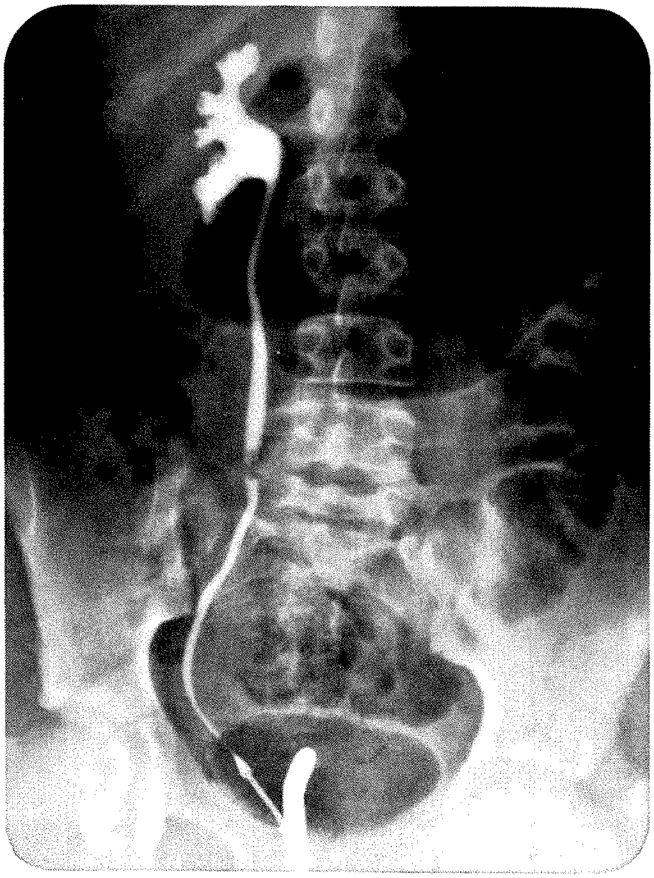

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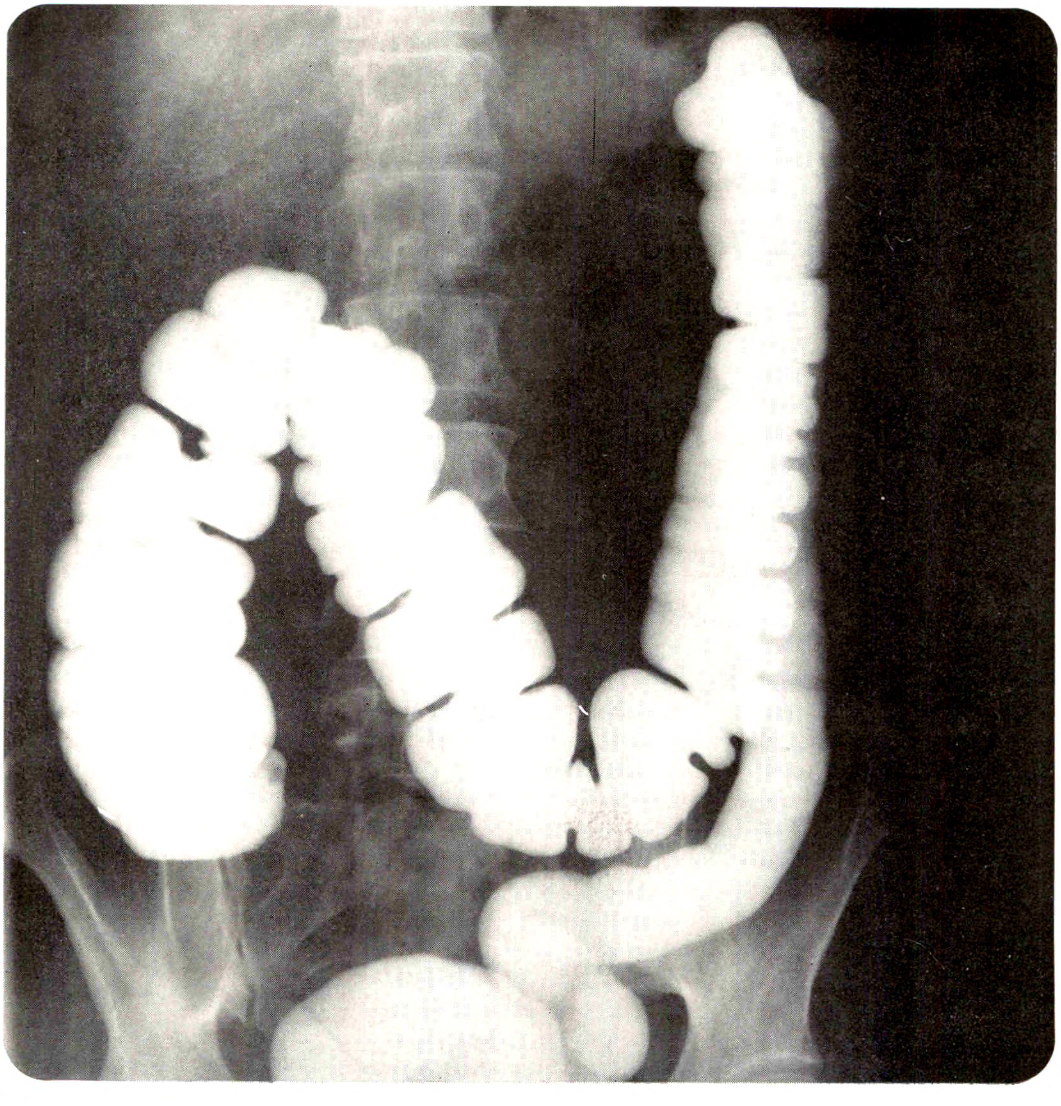

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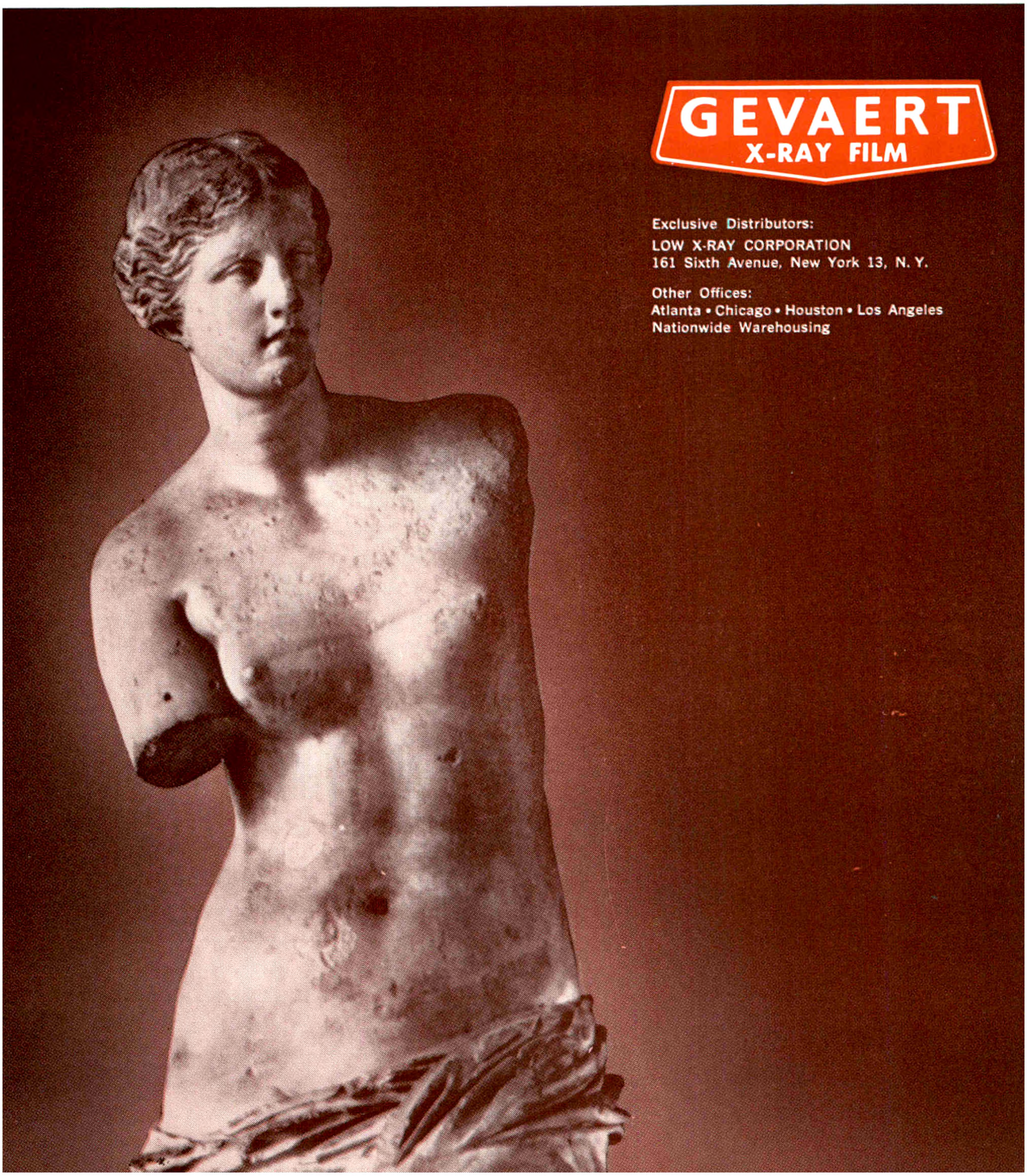

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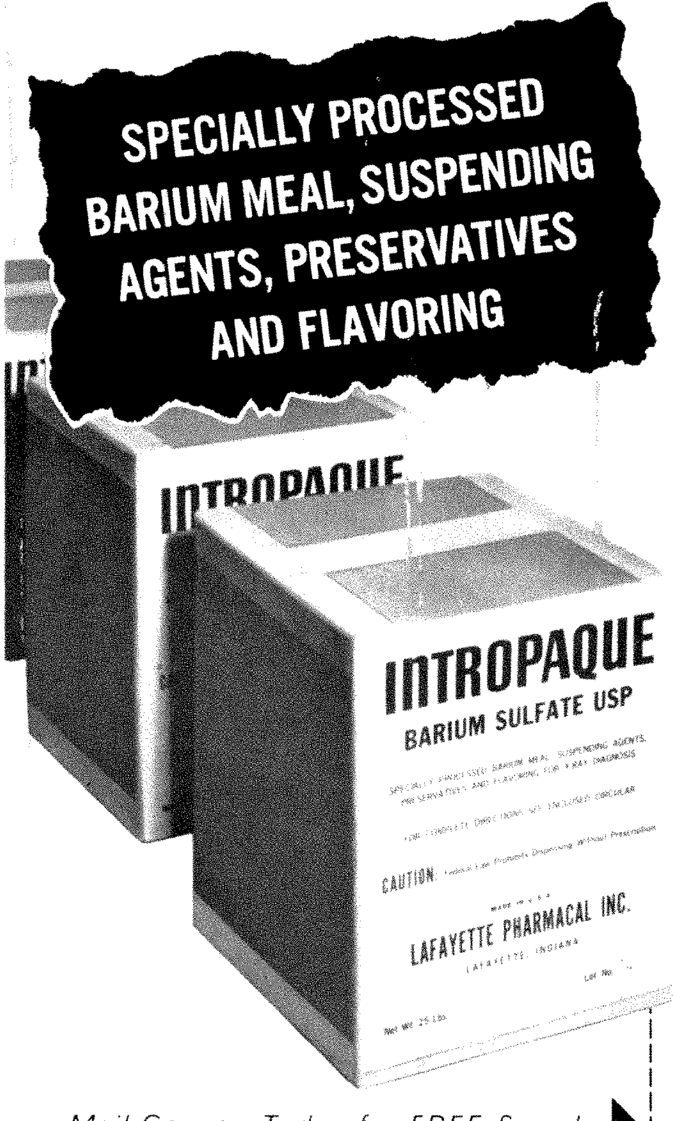
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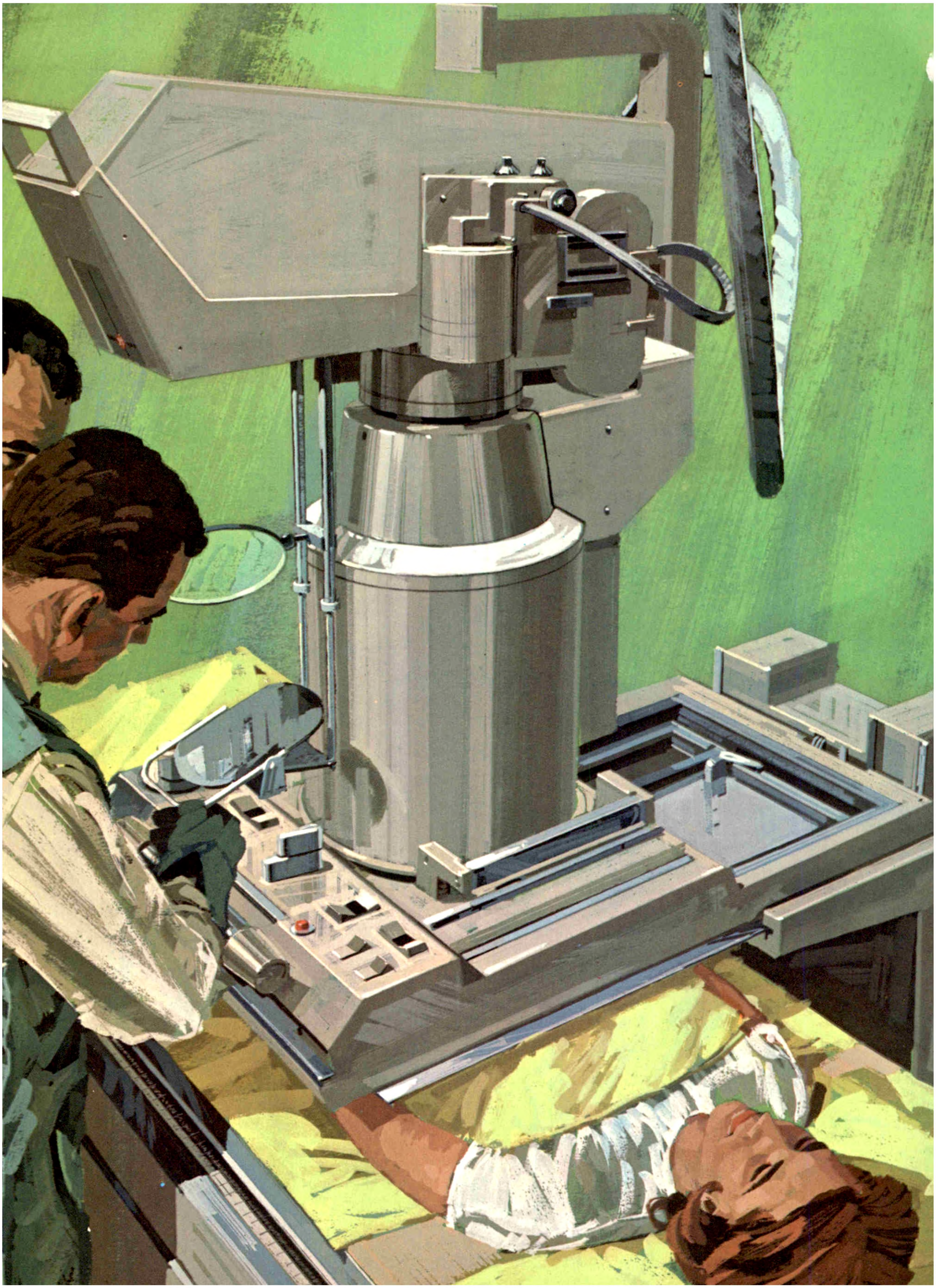

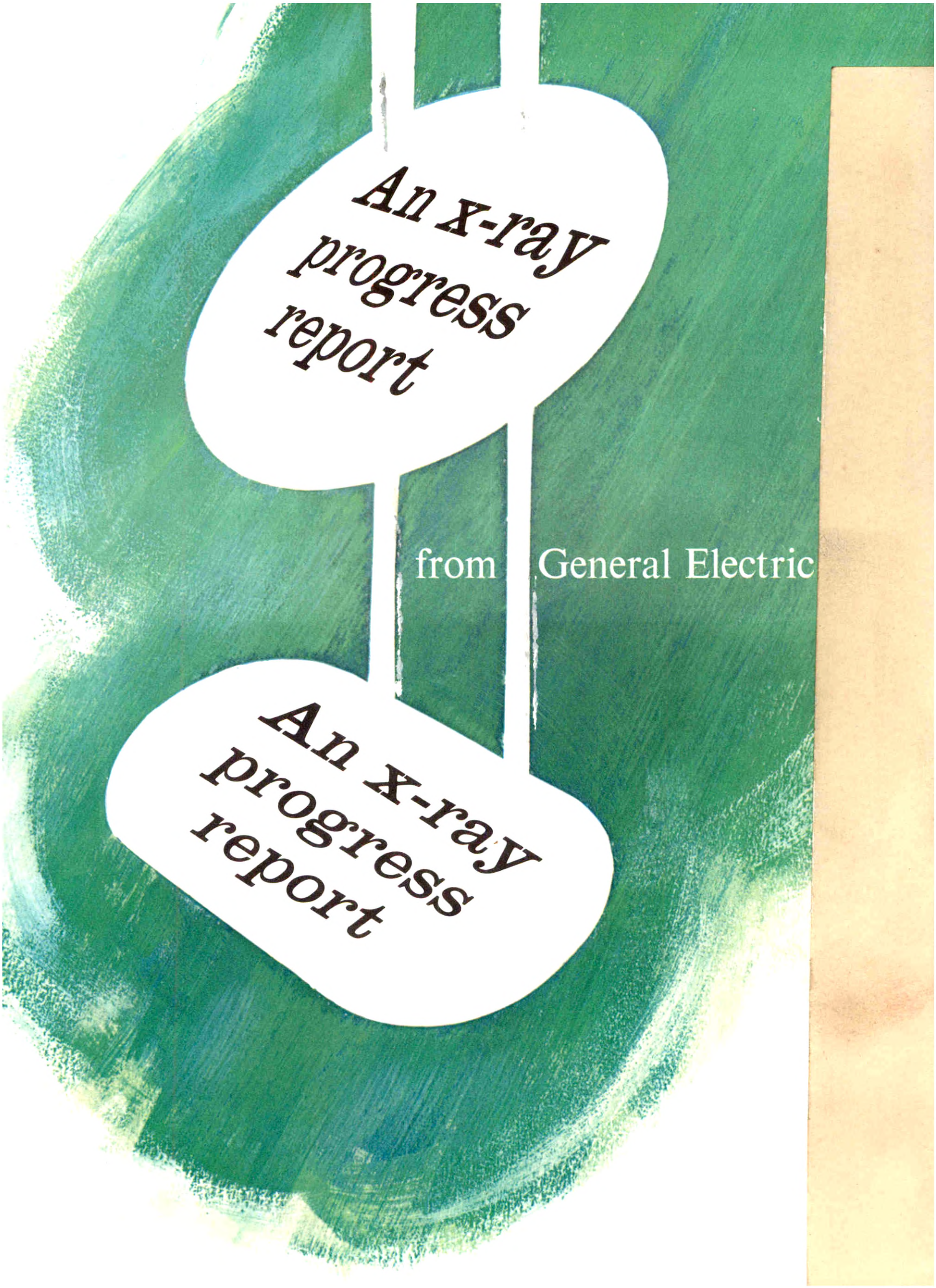

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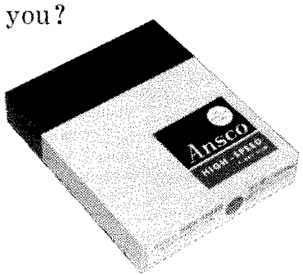

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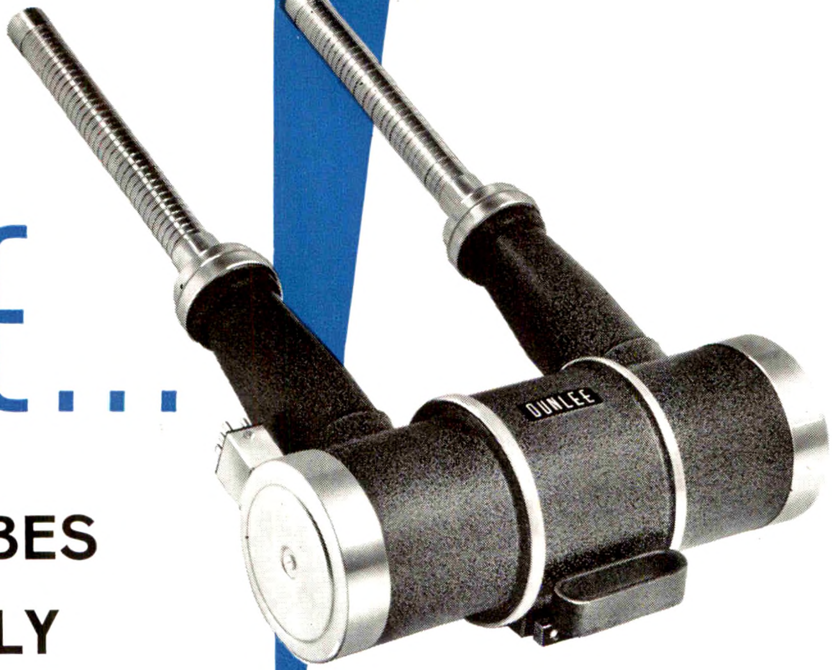

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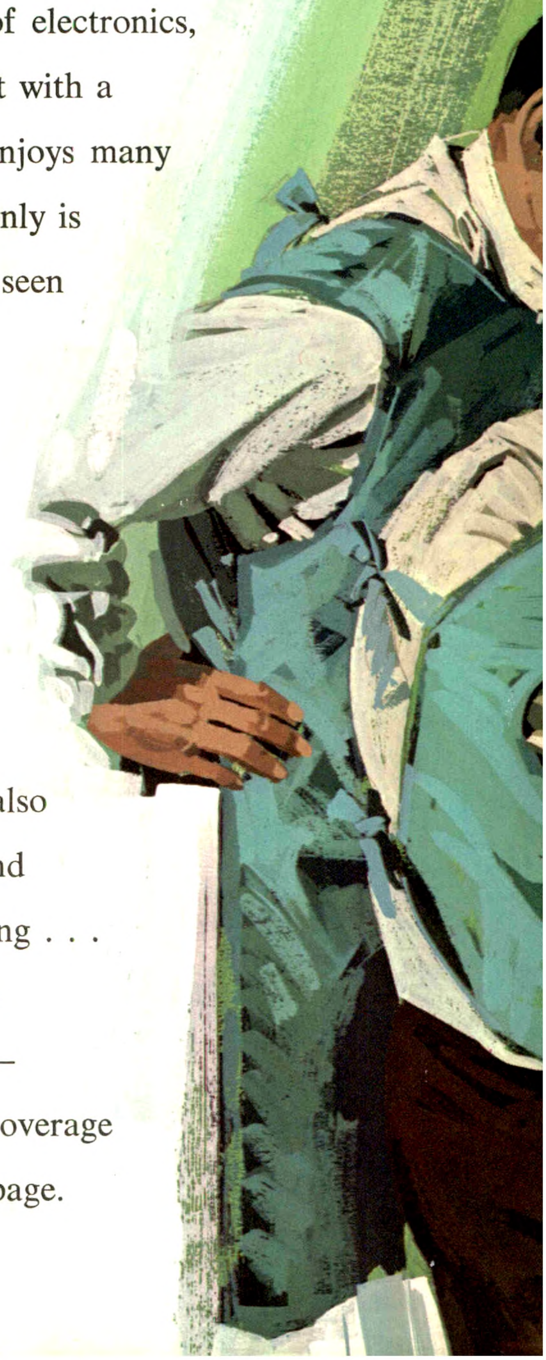

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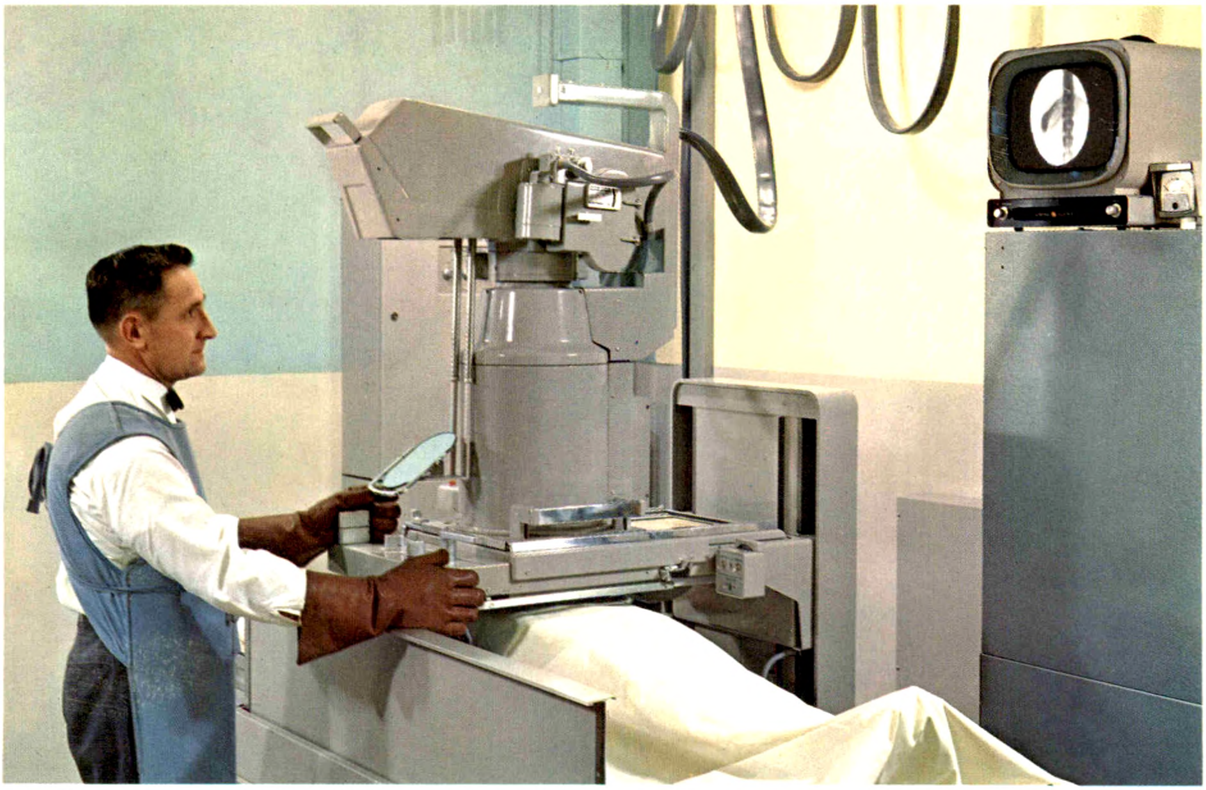

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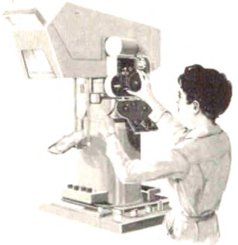

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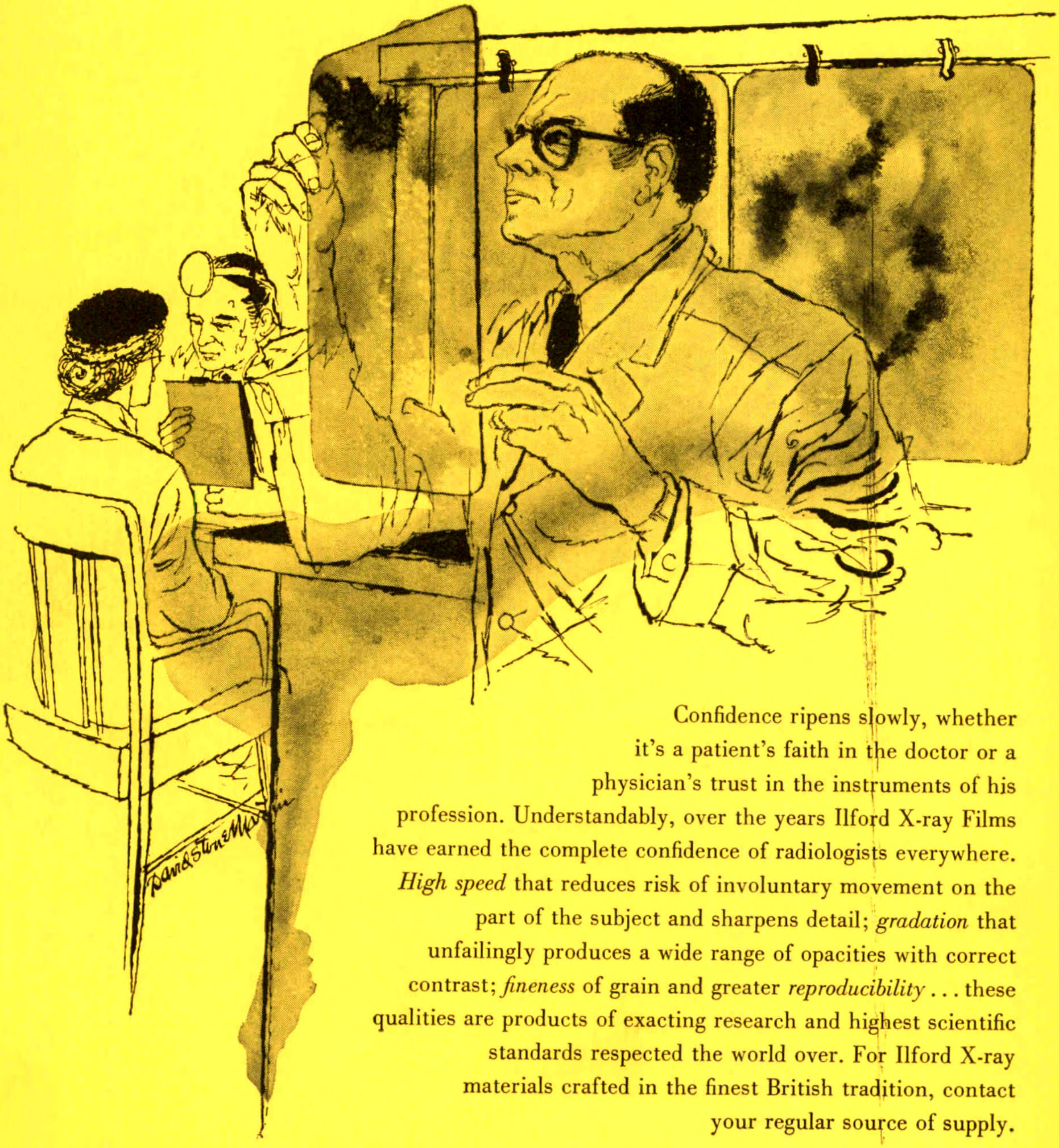

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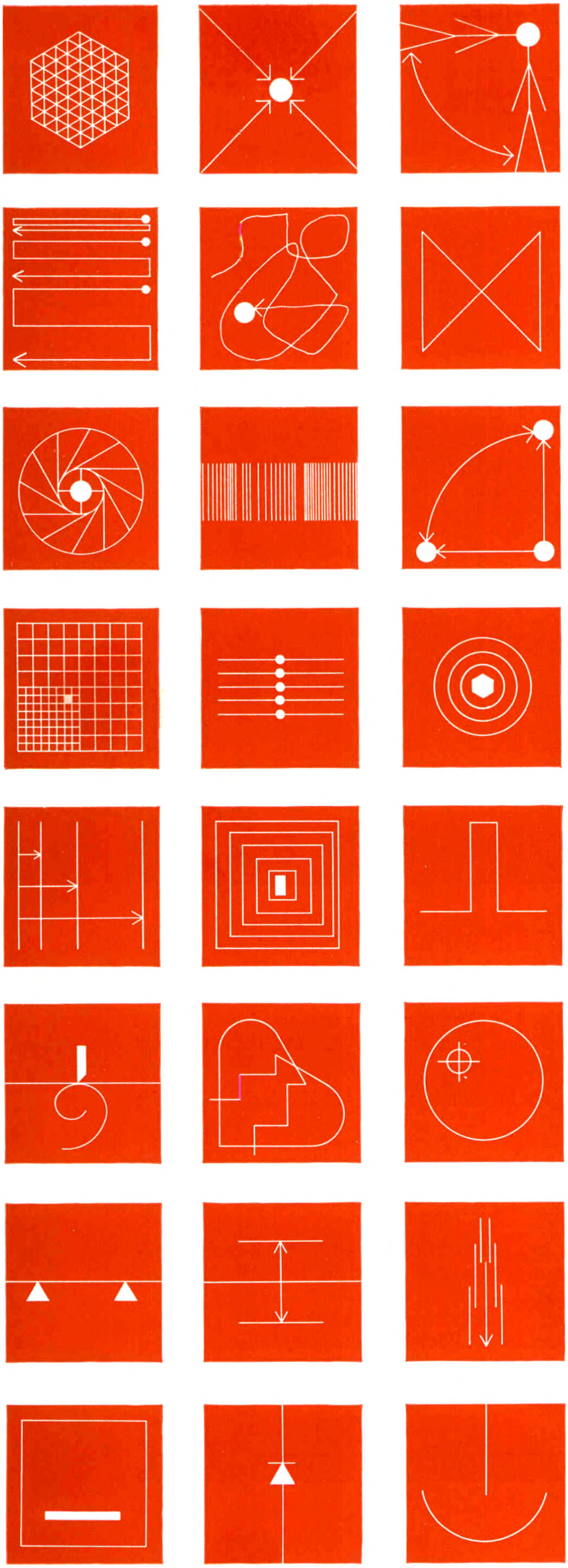

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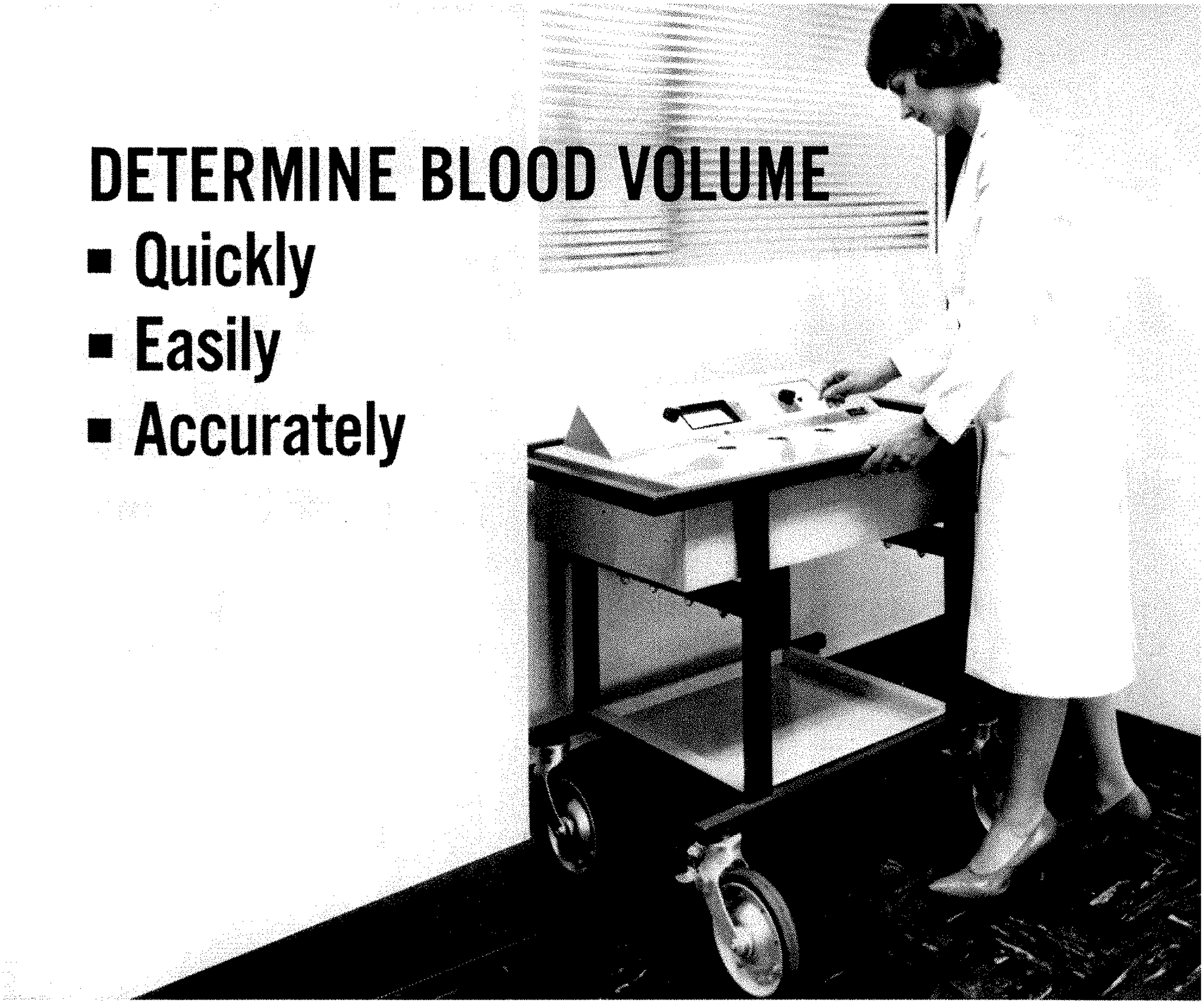

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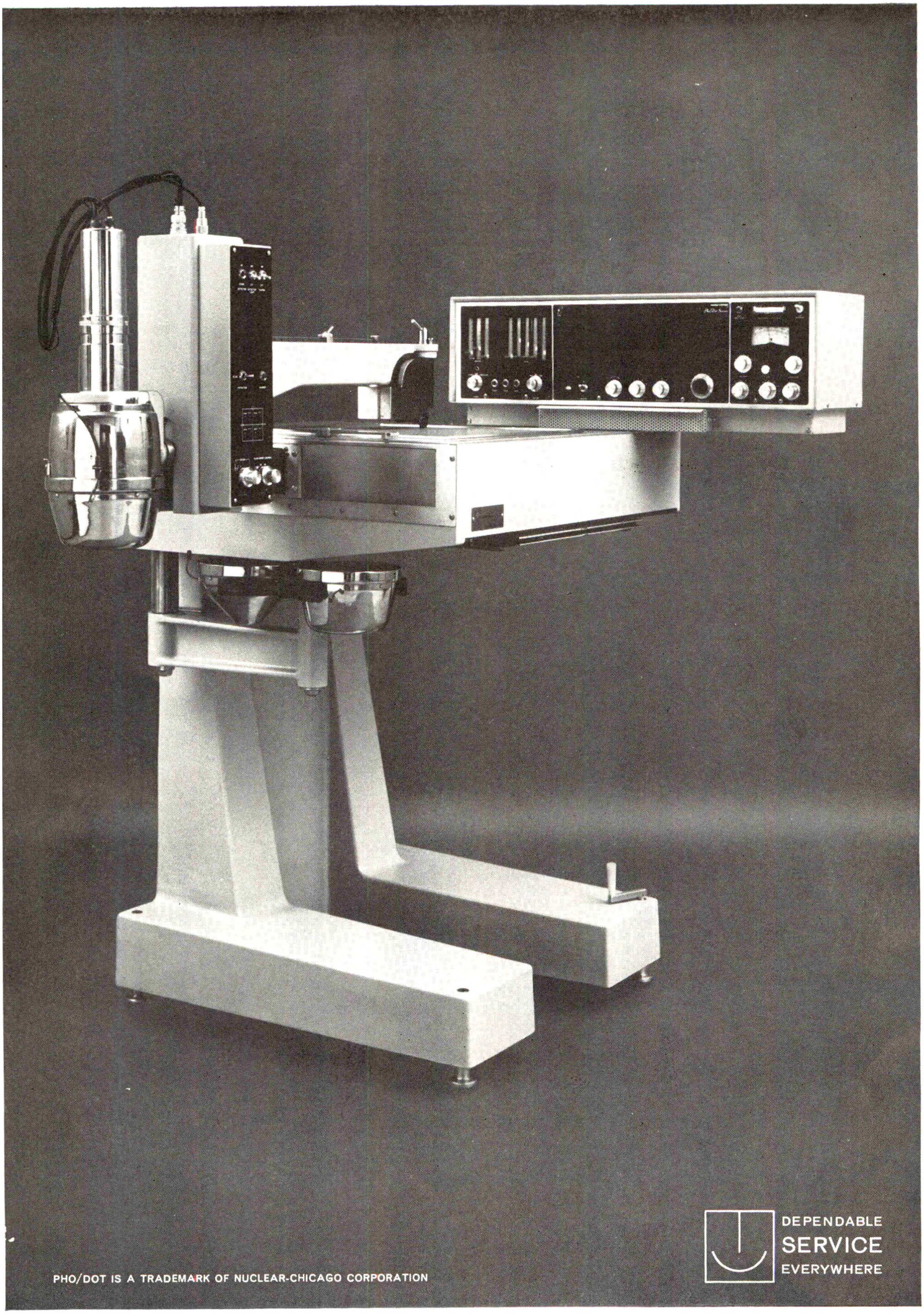
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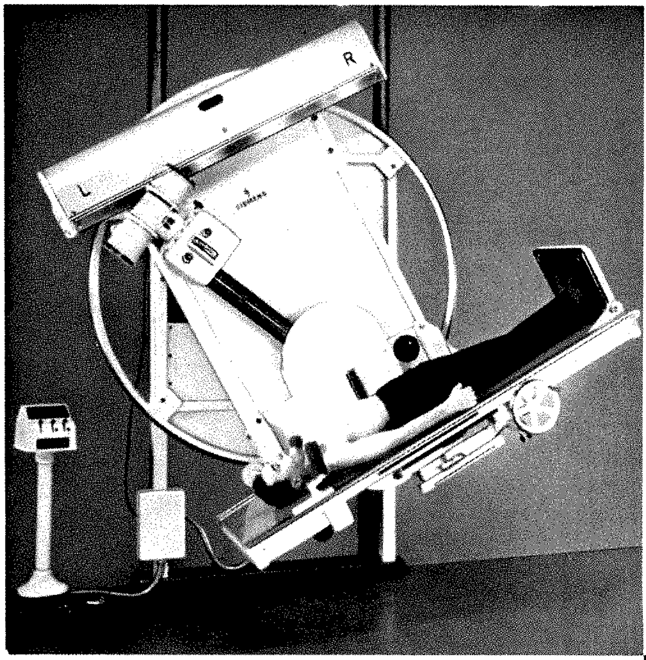

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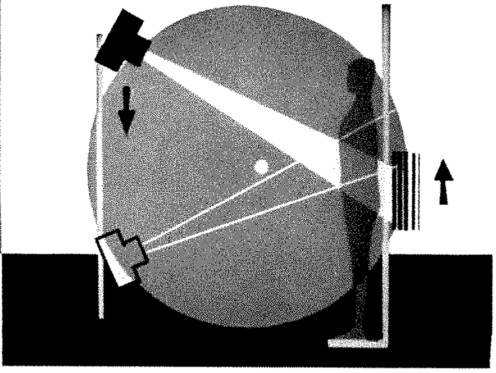

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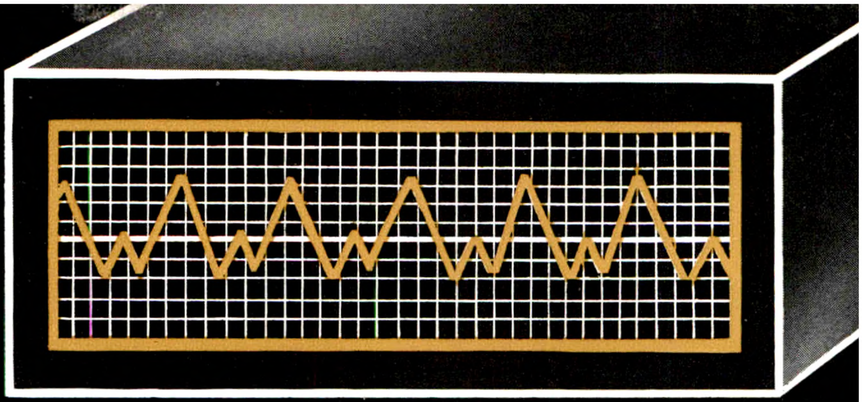

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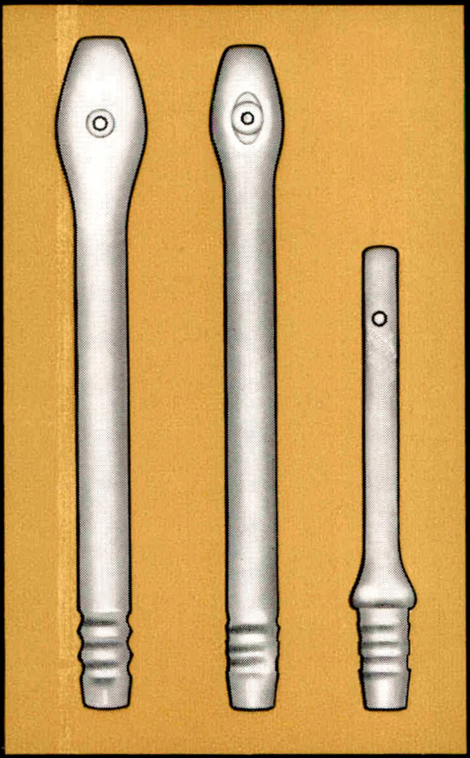

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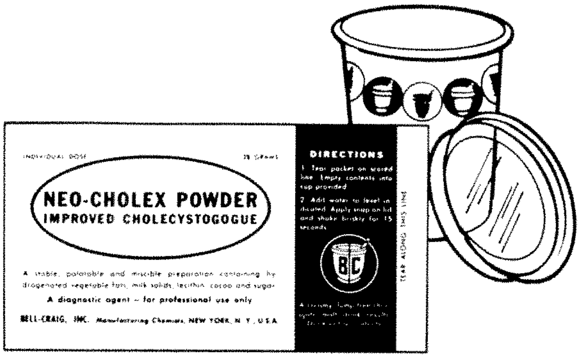
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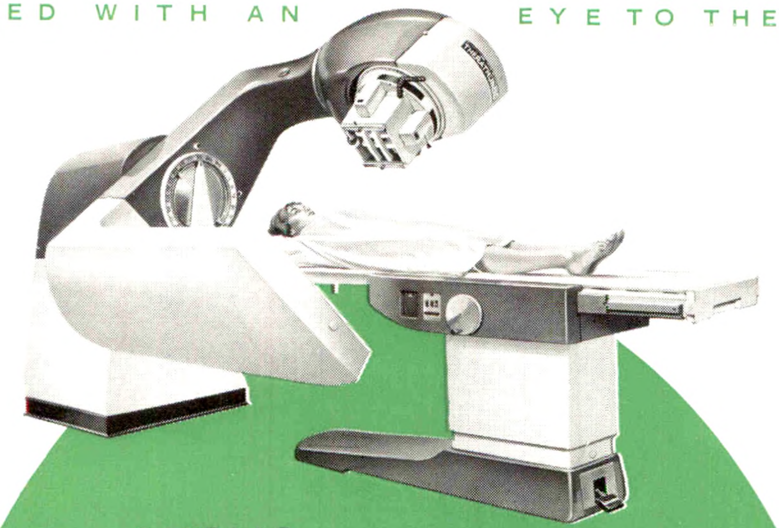

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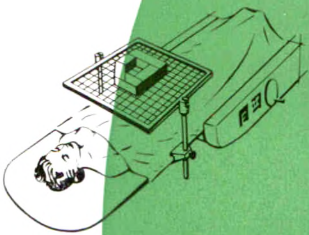

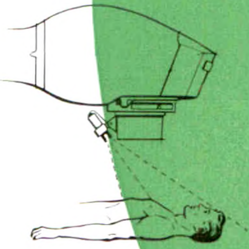

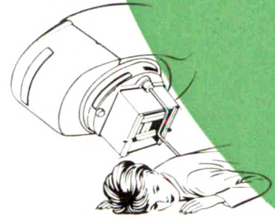

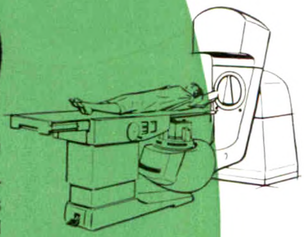

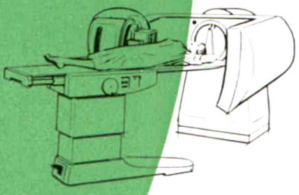

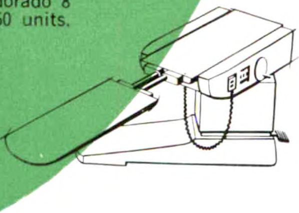

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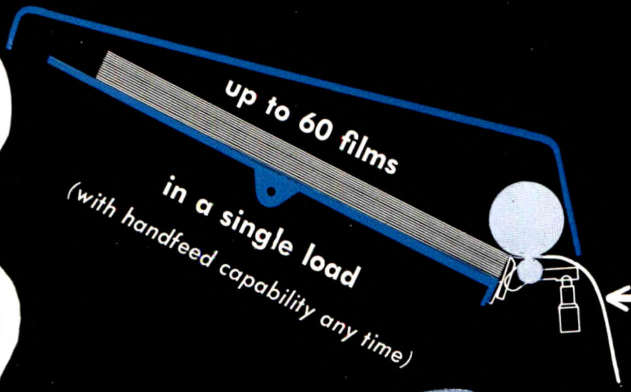

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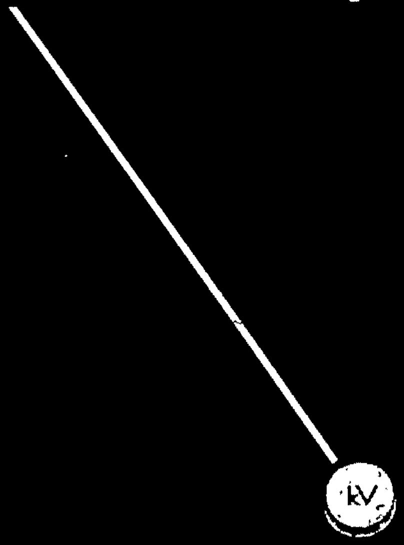

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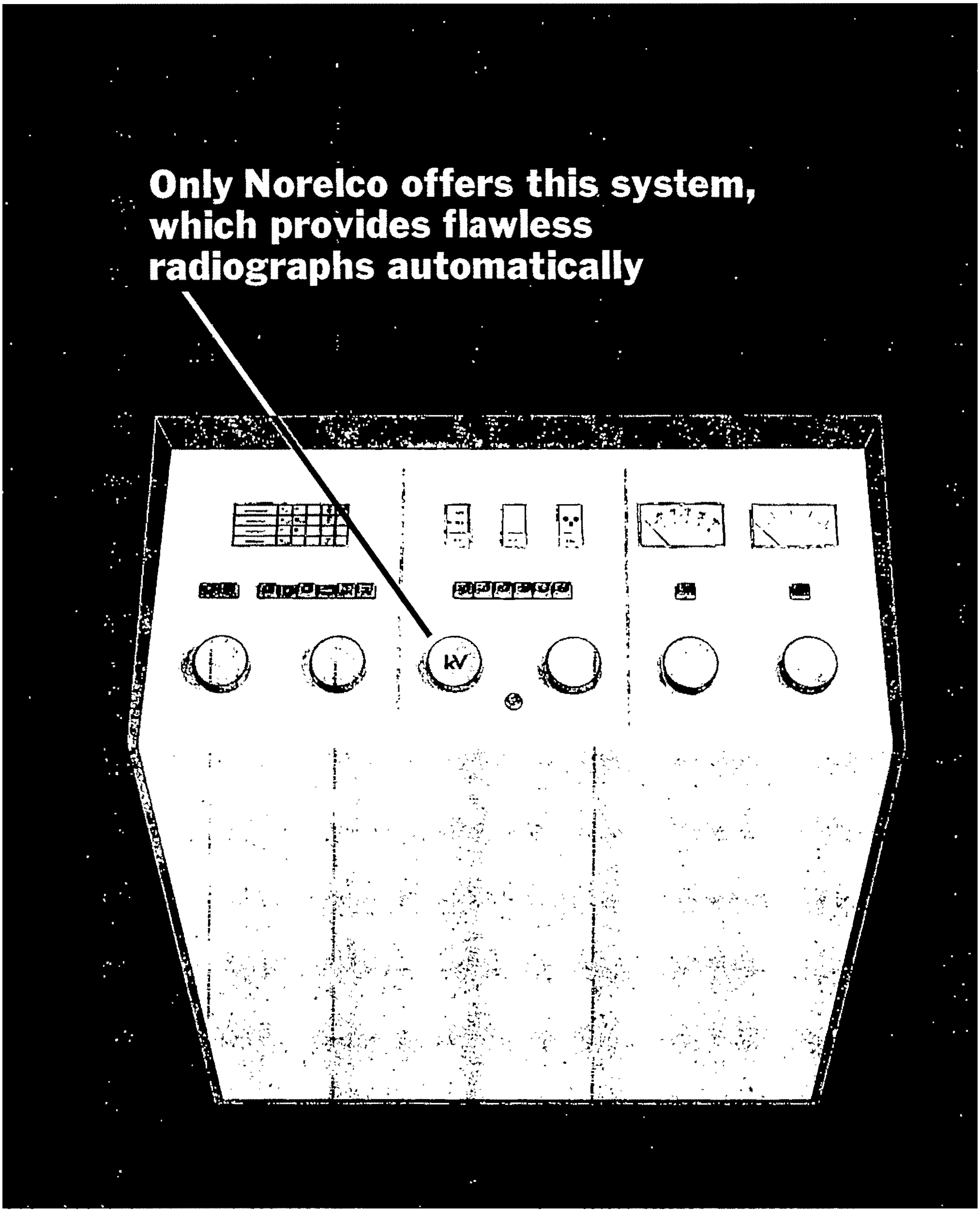
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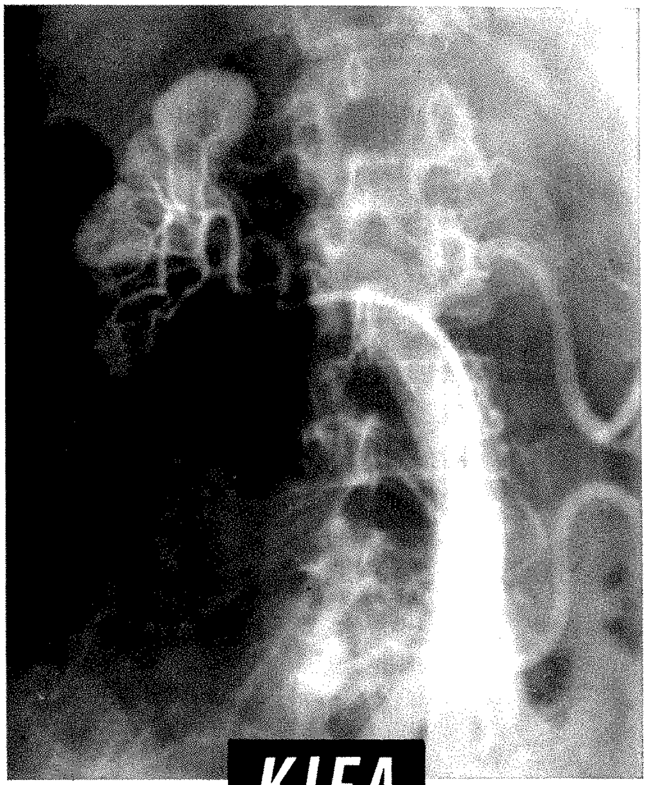

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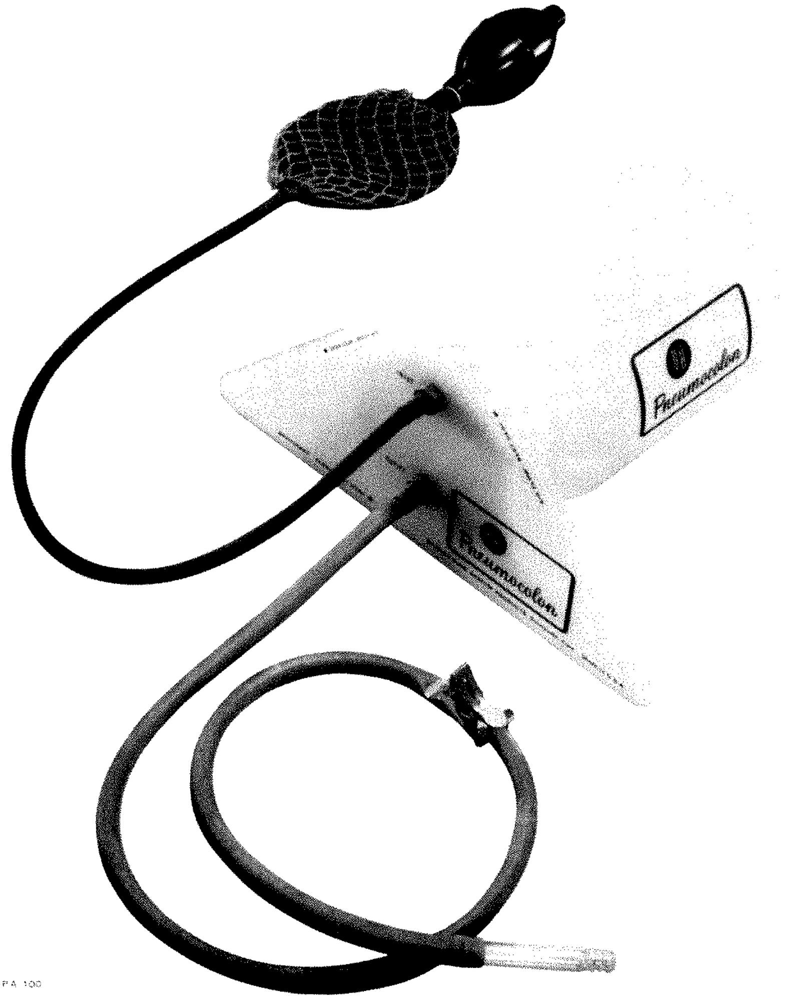

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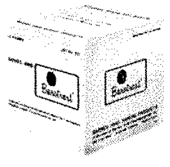

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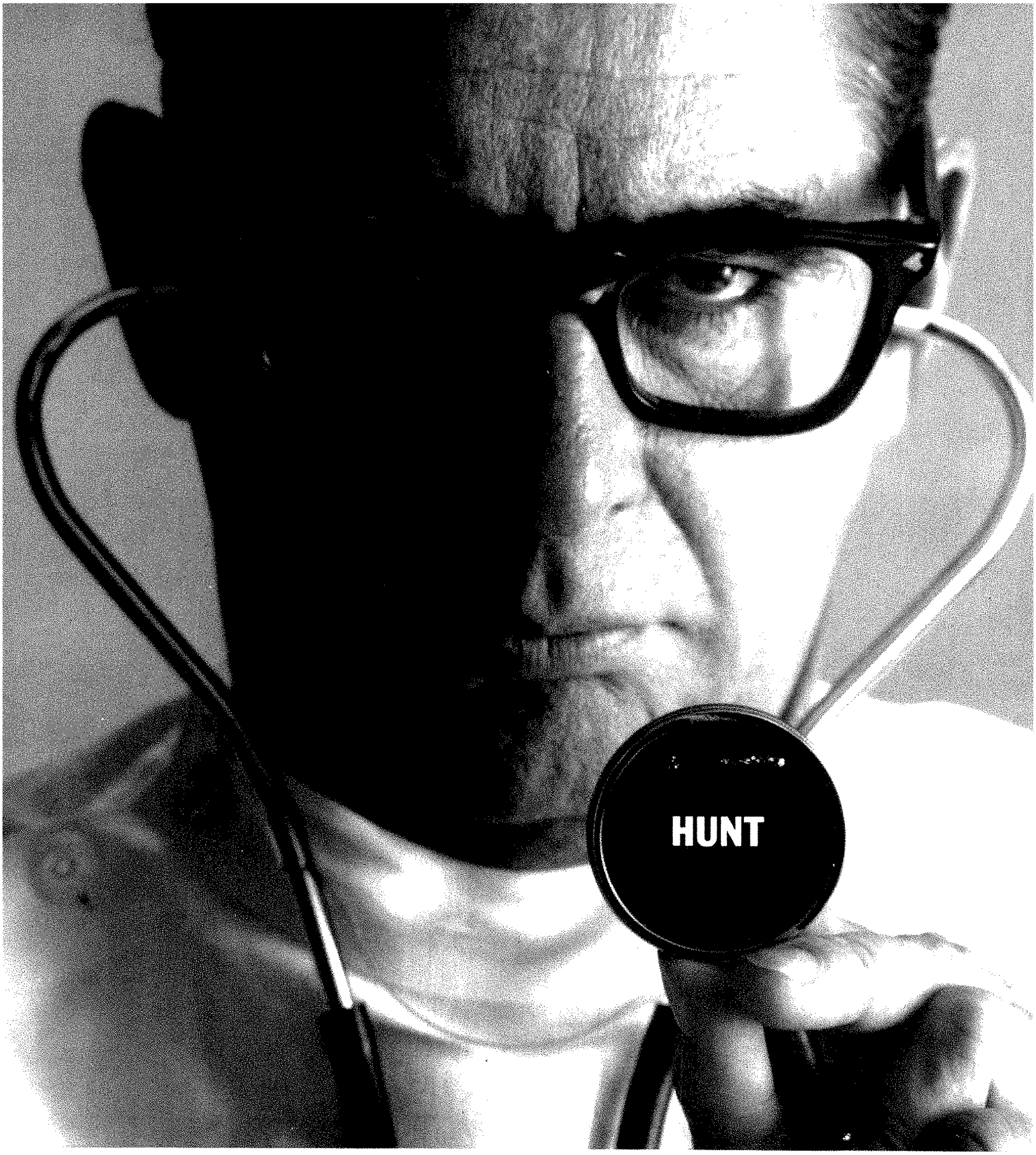

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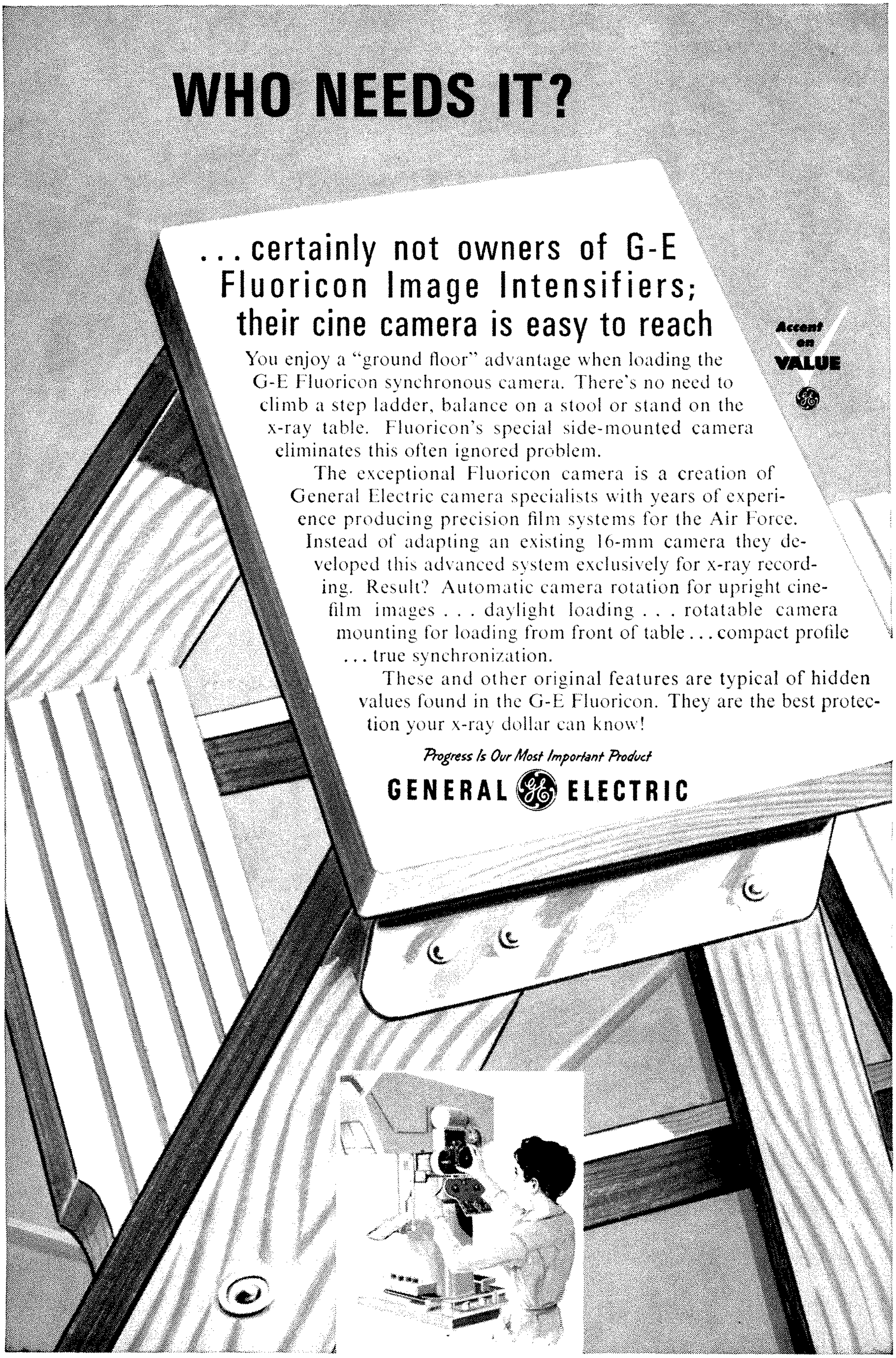

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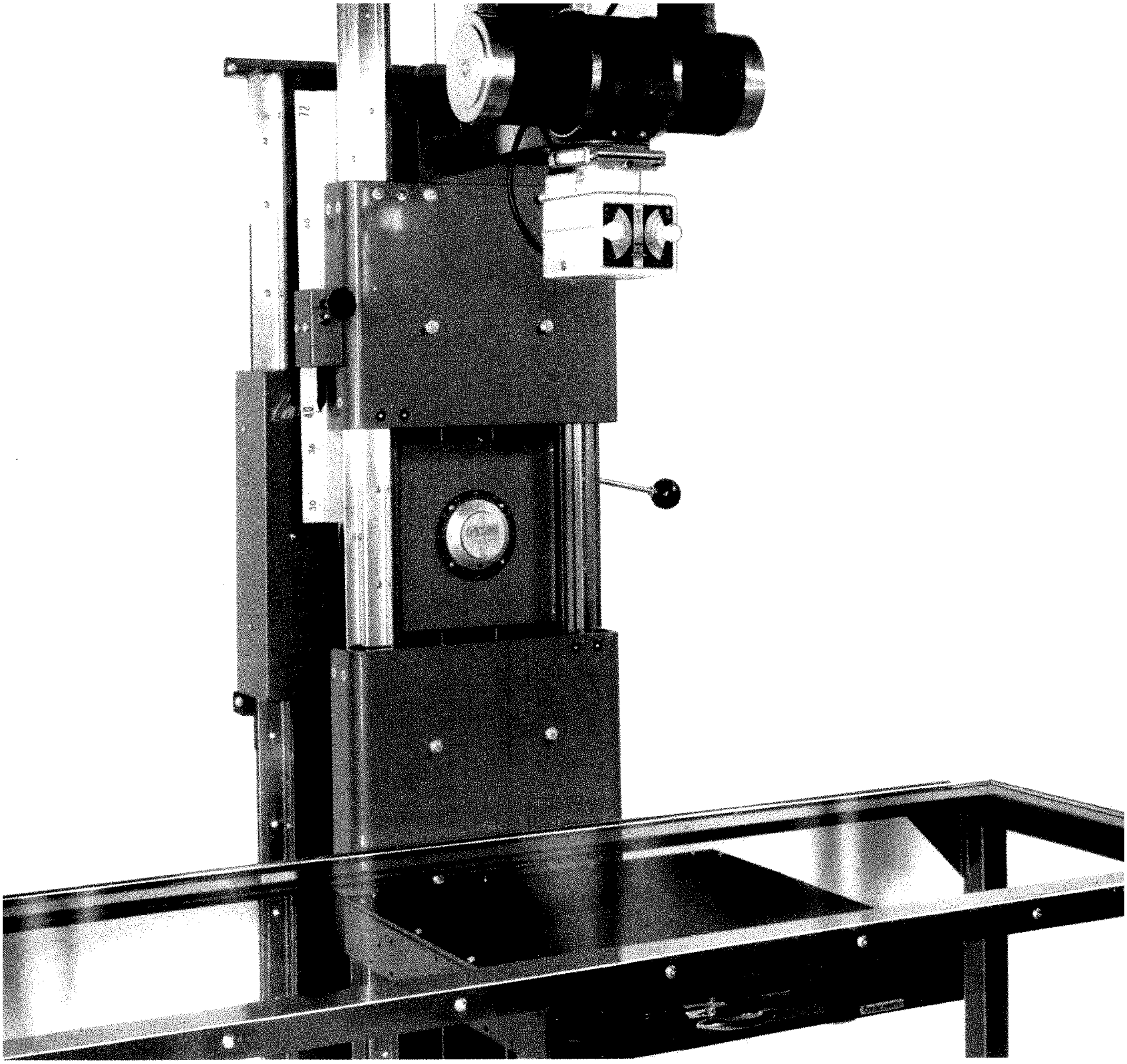

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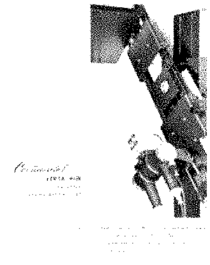

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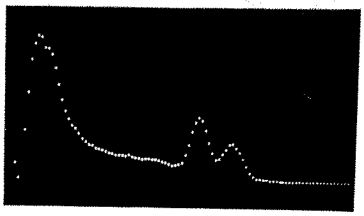

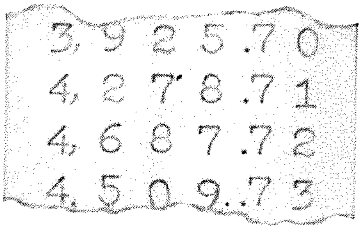

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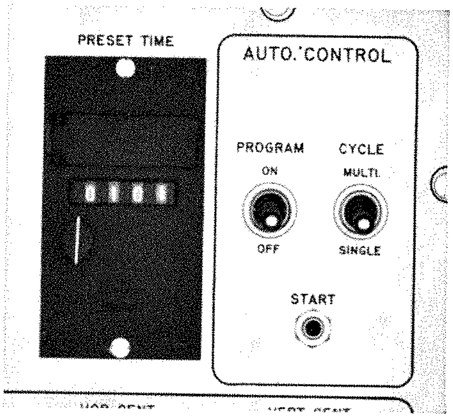

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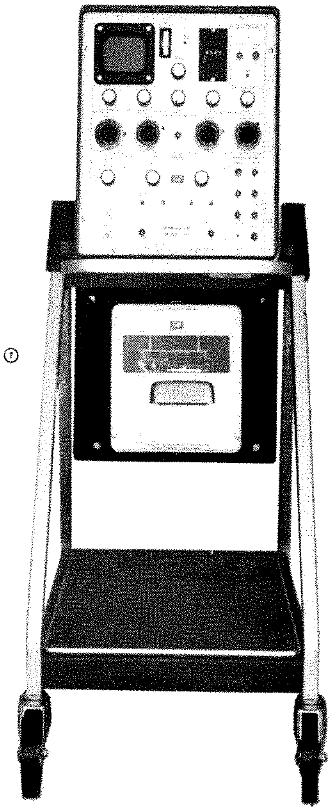

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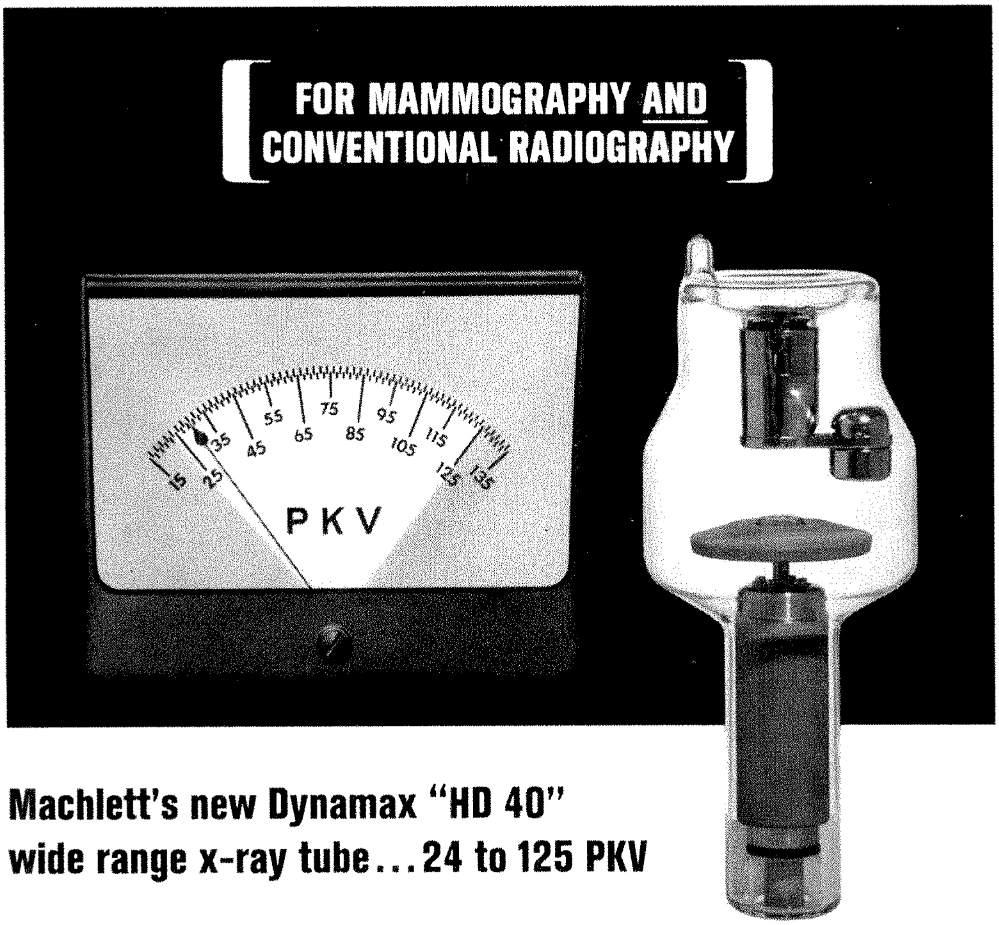

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RADIOLOGY OF PULMONARY CIRCULATION*

CHAMBERLAIN LECTURE—1963

By R. E. STEINER, M.D., M.R.C.P., F.F.R.
LONDON, ENGLAND

FOR this W. Edward Chamberlain Lecture I have chosen the topic of Radiology of Pulmonary Circulation, one of my main interests for many years. This particular subject clearly demonstrates how correlation of radiological, clinical, physiological and pathological data has led to considerable advance in the understanding of the pulmonary circulation.

Dr. Chamberlain has always stressed the importance of physiological thinking in radiological interpretation and it therefore is a great pleasure for me to try and explain how radiology has influenced and advanced our thoughts and understanding of some of the problems of pulmonary circulation and of pulmonary physiology.

IN THIS discussion I will deal primarily with the problems of pulmonary hypertension.

CLINICAL BACKGROUND AND CLASSIFICATIONS

There are three main basic types of pulmonary hypertension:[39,40]

(A) *Passive pulmonary hypertension*, when the pulmonary venous pressure is elevated.

(B) *Hyperdynamic or hyperkinetic pulmonary hypertension* due to increased pulmonary blood flow. This type one usually associates with a shunt across the cardiac septum or a shunt from the aorta to the pulmonary artery.

(C) *Vasoconstrictive pulmonary hypertension*, where there is a diminution in size and sometimes also in number of the pulmonary vascular pathways. This last type is subdivided into (a) vasoconstrictive and (b) obliterative (Fig. 1).

Vasoconstrictive and obliterative pulmonary hypertension are due to lesions occurring on the arterial side of the pulmonary circulation, and for this reason the terms precapillary or arterial pulmonary hypertension are used. In hyperdynamic pulmonary hypertension, too, where there is a left to right shunt, the strain lies on the right side of the heart and pulmonary arteries, and this type, therefore, will also give rise to pulmonary arterial hypertension. By contrast, passive pulmonary hypertension affects primarily the venous side of the pulmonary circulation and the lesions are either in the pulmonary veins or on the left side of the heart. This gives rise to pulmonary venous or postcapillary hypertension.

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* Presented at Temple University School of Medicine and Hospital, Philadelphia, Pennsylvania, February 11, 1963.

(A) The important causes of passive pulmonary venous hypertension are: (1) left atrial obstruction due to mitral valve disease, left atrial tumor or a large ball valve thrombus; (2) left ventricular failure irrespective of the cause; (3) rarely, pulmonary capillary and pulmonary venous disease; and (4) occasionally, constrictive pericarditis.

(B) The main causes of hyperdynamic pulmonary hypertension are: (1) congenital anomalies of the heart with a left to right shunt as for example atrial septal defects, ventricular septal defects, and patent ductus arteriosus or other types of aortopulmonary communications; and (2) diseases where there is an increased pulmonary blood flow associated with a hyperdynamic circulation as for example thyrotoxicosis, severe anemia, beriberi heart disease and very rarely extensive Paget's disease.

(C) The most important causes of vasoconstrictive pulmonary hypertension are (a) in the vasoconstrictive group: (1) hypoxia; (2) response to certain drugs, as for example acetylene choline; and (3) secondary to an increased pulmonary blood flow, particularly in congenital heart disease with a left to right shunt; and (b) in the obliterative group: (1) thromboembolism; (2) tumor embolism; (3) bilharzia; (4) various types of arteritis, as for example polyarteritis or disseminated lupus erythematosus; (5) various causes of diffuse and extensive pulmonary fibrosis; (6) congenital heart disease with reversal of shunt from right to left, the so-called "Eisenmenger's reaction;" and (7) idiopathic primary pulmonary hypertension (very rare).

ROENTGENOLOGIC FINDINGS AND CORRELATION WITH PATHOLOGIC PHYSIOLOGY

The most important feature on plain chest roentgenograms in the hyperkinetic group is dilatation of the main pulmonary arteries and their smaller branches well out into the smaller peripheral divisions, thus providing an over-all picture of pulmonary hyperemia, which is more or less uniform throughout the lung fields. The degree of pulmonary hyperemia largely depends on the magnitude of the left to right shunt. Once the left to right shunt has been corrected surgically and the excessive blood flow through the lungs has decreased, the size of the pulmonary artery and smaller branches diminishes and pulmonary hyperemia is no longer demonstrated (Fig. 2, *A* and *B*). Together with pulmonary artery

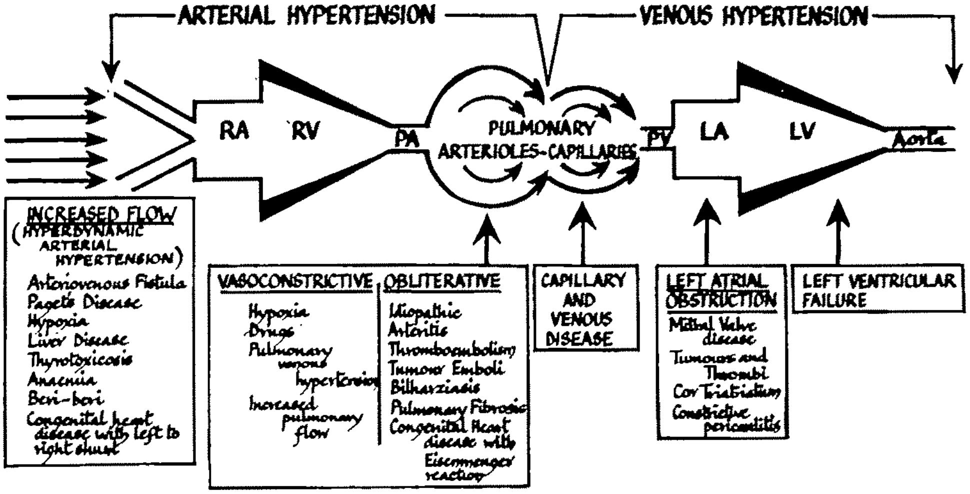

Fig. 1. Diagrammatic representation of the pulmonary circulation. The various causes of pulmonary arterial and pulmonary venous hypertension are listed. (By courtesy of Messrs. Churchill and Co., London.)

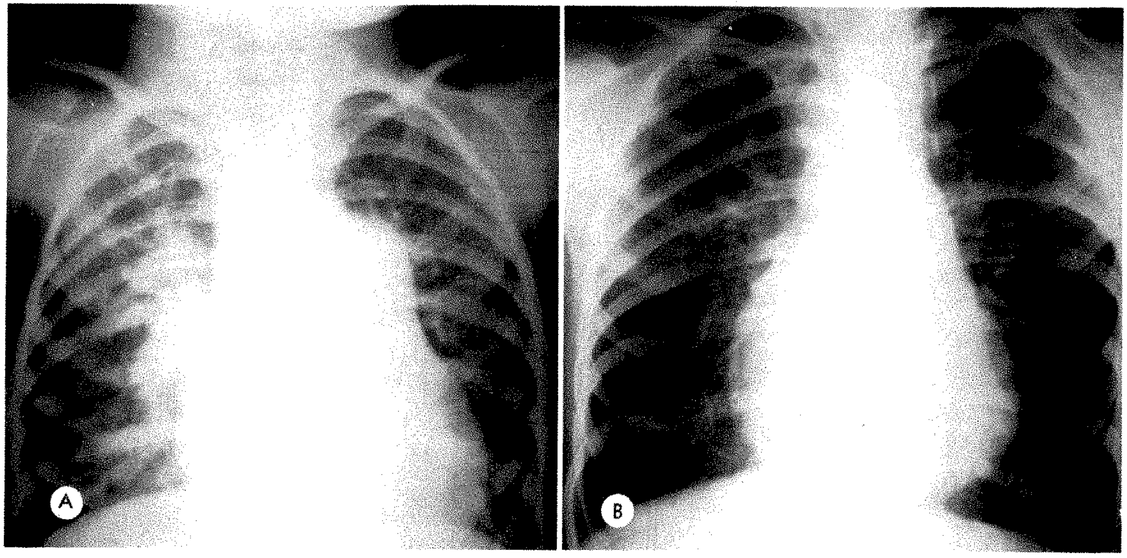

Fig. 2. (*A*) July 10, 1958: A young child with ventricular septal defect. Preoperative chest roentgenogram demonstrates the very large pulmonary artery and distended smaller pulmonary branches right out into the peripheral lung fields. (*B*) August 4, 1963: Same patient 1 year after the ventricular septal defect had been closed. Note the diminution in heart size, pulmonary artery and branches with disappearance of the pulmonary plethora.

dilatation there will always be appreciable right ventricular enlargement and this too regresses once the excessive pulmonary blood flow has been stopped. These changes, particularly regression in the size of the pulmonary vessels together with diminution in heart size postoperatively, will only occur after an appreciable lapse of time, sometimes only after many months.

One usually associates the greatest distention of the main pulmonary artery and branches with atrial and ventricular septal defects and to a less extent with a patent ductus arteriosus or aortopulmonary window. In ventricular septal defects, ductus and aortopulmonary communications, in addition to the right sided cardiac enlargement, there will also be left sided cardiac enlargement.

In a number of patients with a large left to right shunt, a reactive vasoconstrictive pulmonary arterial hypertension develops. There are probably two factors responsible; a truly reactive vasoconstriction of the smaller peripheral arteries and, secondly, obliteration of the vascular bed due to gross intimal thickening and arterial narrowing with thrombosis.[14,17] On the chest roentgenogram, too, this vasoconstriction may be apparent, particularly if pulmonary hypertension is severe and the shunt has reversed.[36,37] This pattern is sometimes described as the "Eisenmenger reaction" and is seen in patients with atrial and ventricular septal defects and occasionally in patients with a persistent ductus arteriosus. On the plain chest roentgenogram there is marked enlargement of the heart, particularly of the right ventricle; the main pulmonary artery and main branches are grossly dilated, chiefly the first and second divisions, but there is remarkable vasoconstriction with pruning of the small peripheral branches, giving a distinct impression of pulmonary ischemia in the peripheral lung fields. This discrepancy between dilatation of the main artery and main branches and the peripheral ischemia is quite characteristic of the Eisenmenger reaction in congenital heart disease (Fig. 3, *A-D*).

I would now like to discuss the roentgenologic findings of pulmonary venous hypertension in contrast to pulmonary ar-

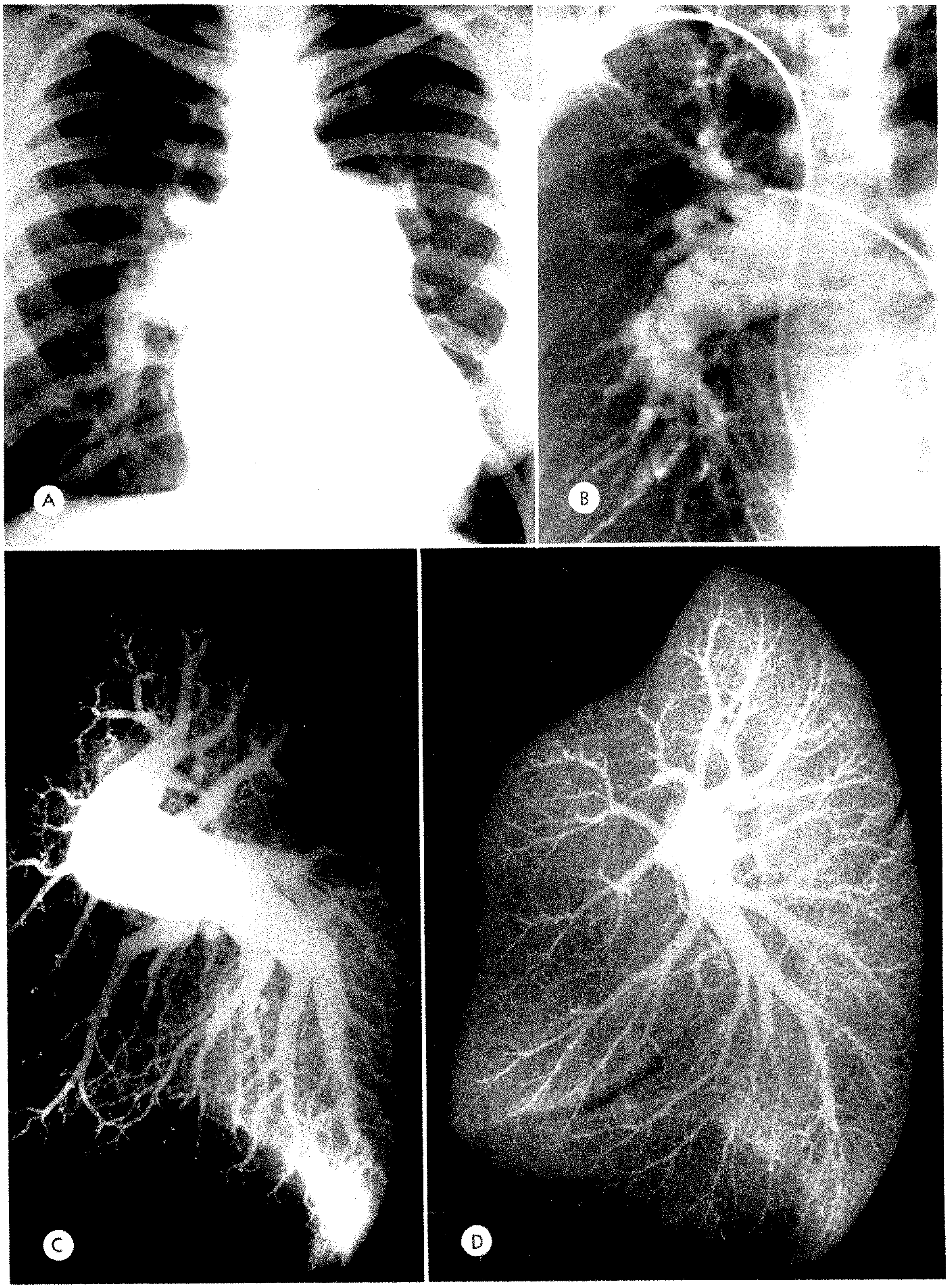

FIG. 3. (*A*) Chest roentgenogram of a patient with atrial septal defect, high pulmonary artery pressure and increased pulmonary vascular resistance (Eisenmenger's reaction). The right ventricle is enlarged, and there is marked dilatation of the main pulmonary artery and main branches with relative ischemia of the

terial hypertension with an increased pulmonary blood flow. Pulmonary venous hypertension is most common in acquired heart disease and the causes for it have already been mentioned. Before analyzing the roentgenologic features of pulmonary venous hypertension I must mention pulmonary arterial hypertension developing secondary to pulmonary venous hypertension. An elevated pulmonary venous pressure will inevitably lead to an elevation of the pulmonary arterial pressure. This development of pulmonary arterial hypertension occurs particularly in patients with mitral valve disease and left ventricular failure.[17] The first roentgenologic observations of pulmonary arterial changes in mitral valve disease were made by Goodwin, Steiner and Lowe[16] in 1952, and were subsequently confirmed by many other workers.[3,4,9] The development of pulmonary arterial hypertension in these conditions is probably secondary to the elevated pulmonary venous pressure and can either be vasoconstrictive or obliterative.[17]

If one analyzes the appearance on the plain chest roentgenogram, one will note that with increasing pulmonary artery pressure there is concomitant dilatation of the main pulmonary arteries and main first and second division branches,[9,25] whereas the small peripheral arteries appear to be narrowed. This arterial narrowing of the small branches is regional, affecting the lower and mid-zones of the lung more so than the upper zones, where the caliber of the arteries remains normal.[9] It was suggested by Doyle and his co-workers[9] that narrowing of the pulmonary arteries in the lower zones of the lung occurred in response to the elevated pulmonary venous pressure, which had been elevated to a critical level above the plasma osmotic pressure by the difference of the hydrostatic pressure between the bases of the lungs and the apices. This differential reaction of arterial constriction leads to a selective vasoconstriction and deviation of blood from the lower zones of the lungs to the upper zones. In congenital heart disease where the pulmonary venous pressure is not significantly elevated, this selective vascular response does not occur (Fig. 4). These findings and suggested physiological explanation have since been corroborated by Dollery and West,[7] who measured the pulmonary blood flow with carbon dioxide labelled oxygen 15. These workers were able to show that in patients with mitral stenosis the blood flow is reduced in the lower zones, but not in the upper zones of the lungs, a situation which is exactly the reverse to the normal physiology in man where the blood flow to the upper zones is smaller than to the lower zones.[7]

On the plain chest roentgenogram, this differential effect of vasoconstriction of the small pulmonary arteries may be difficult to interpret since the small arterial branches, particularly in the lower zones, are hard to differentiate from other vascular structures;[37] but by using contrast studies, particularly selective pulmonary arteriography, this differential effect of vascular response can be clearly demonstrated (Fig. 5). Selective angiography can be of great help in assessing the more detailed anatomical variations, as these studies give satisfactory information about the very small arterial and venous branches[26,30] (Fig. 6, *A* and *B*). The combination of selective injections with cineangiography may provide valuable information in assessing circulation time in segmental areas of the lung and

←

peripheral lung fields. (*B*) Pulmonary arteriogram of the right pulmonary artery demonstrates the discrepancy between the size of the main artery and small branches, with inadequate filling of the very small peripheral branches. (*C*) Postmortem injection specimen of the left pulmonary arteries of a patient with atrial septal defect who died with severe pulmonary hypertension. There is gross dilatation of the main pulmonary artery and main branches. Some of these branches are tortuous, but there is a very distinct lack of background filling of the very small peripheral branches. Compare this appearance with *D*, which is a normal pulmonary arteriogram of the left lung injected in the same way as *C*.

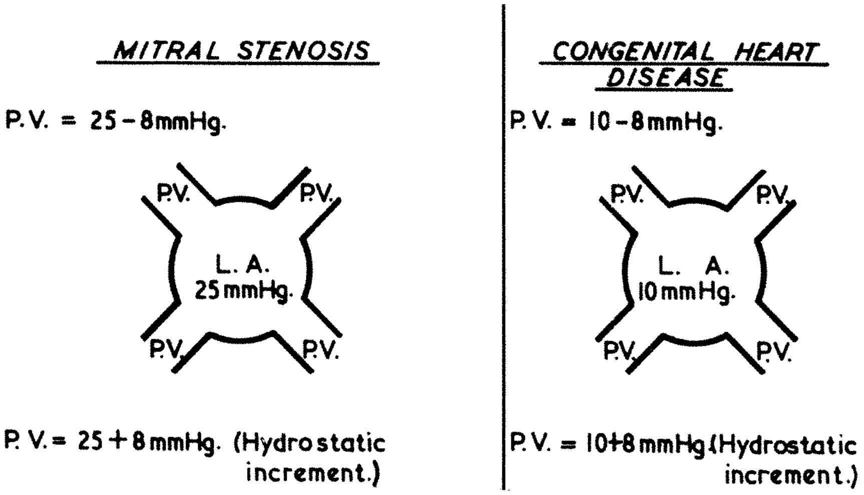

Fig. 4. Diagrammatic representation of the hemodynamic state of (*left*) patient with mitral stenosis and a high pulmonary venous pressure and (*right*) patient with congenital heart disease and a normal venous pressure. In mitral stenosis the pulmonary venous pressure is elevated. In the erect position the hydrostatic increment between the base and apex of the lung when added to the already elevated pulmonary venous pressure raises the level to a critical point which will result in inevitable pulmonary edema. This elevation of the pulmonary venous pressure to such critical levels is probably responsible for the reflex vasoconstriction in the lower and mid-zones of the lungs, which leads to deviation of blood flow to the upper zones. In congenital heart disease, this mechanism is not invoked since the pulmonary venous pressure is at normal levels. (By courtesy of the *British Journal of Radiology*.)

thus demonstrate abnormalities of function.[26] Additional confirmation for this concept was produced by Doyle and co-workers[9] and Harrison,[22] using pathological material for their investigation. Post mortem pulmonary artery injections with contrast medium demonstrated the differential response in the lower and upper zone peripheral arteries very clearly. On histological examination, too, a distinct muscular hypertrophy of the lower zone arteries was seen, whereas the upper zone arteries appeared normal. The small pulmonary veins were affected in the selective way in a similar fashion. In addition to these muscular changes, the large elastic pulmonary

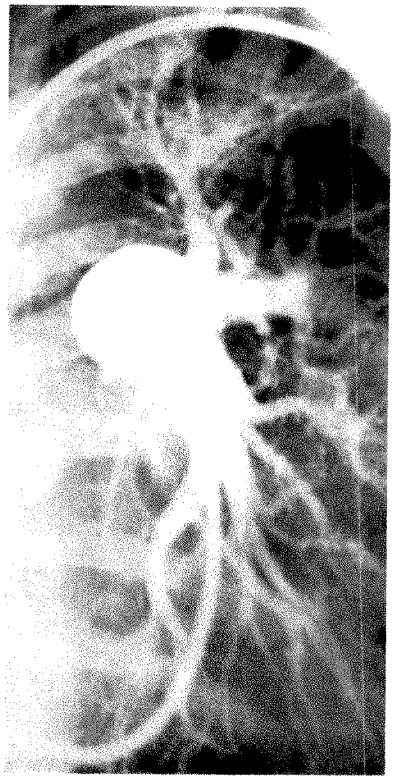

Fig. 5. A left pulmonary arteriogram of a patient with mitral heart disease and severe pulmonary hypertension. Note the dilatation of the left main pulmonary artery, the satisfactory normal filling of the smaller branches in the upper zones, but the very narrow constricted lower lobe arteries with inadequate filling of the small segmental branches.

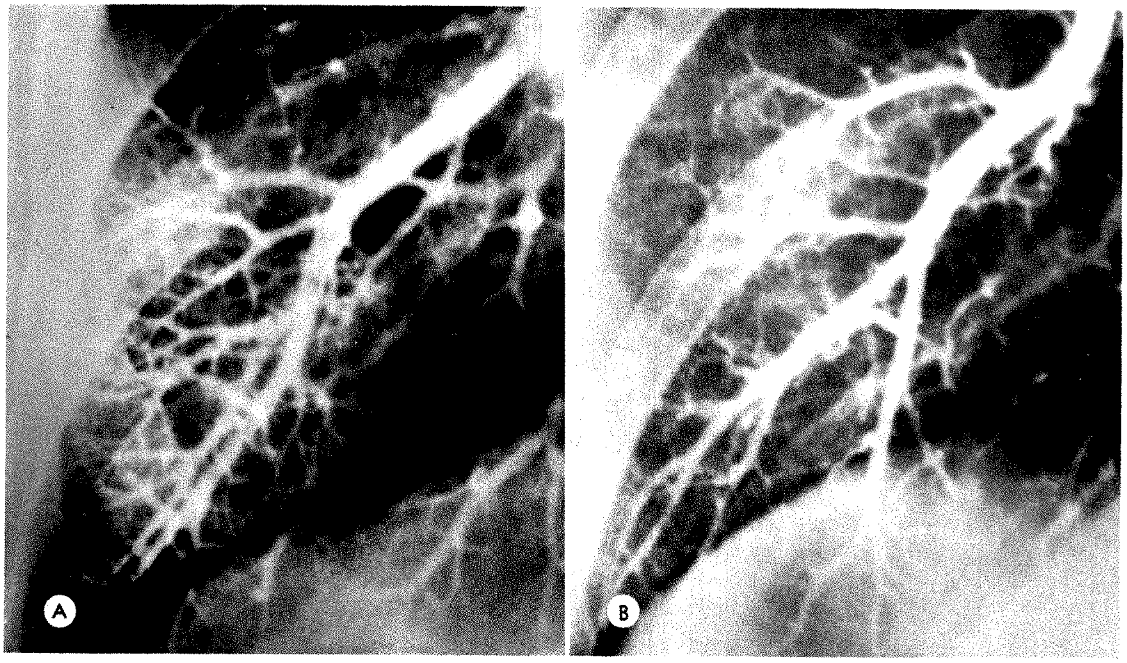

FIG. 6. (*A*) Selective pulmonary arteriogram of right lower lobe of a patient with mitral heart disease with a normal pulmonary artery pressure. Note good filling of the small peripheral branches. (*B*) Another patient with mitral heart disease and severe pulmonary hypertension. Note the inadequate filling of the smaller segmental branches.

arteries occasionally showed evidence of severe atheroma and thromboembolic occlusion, particularly in the lower zones of the lungs.

I will now turn to a discussion of the venous component of pulmonary hypertension and the roentgenological interpretation. The roentgenographic appearance is best considered under two headings: (1) findings which are due to changes in the pulmonary veins and (2) those affecting the pulmonary parenchyma.

It has been shown by Doyle and coworkers[9] and Simon[35] that, in patients with mitral valve disease and an elevated pulmonary venous pressure, the upper lobe veins on plain chest roentgenograms, angiographic studies or laminagrams are either of normal caliber or dilated, particularly if the venous pressure is high, whereas the lower lobe veins are often narrowed. It appears that these selective changes in caliber of the veins occur when the pulmonary venous pressure has reached a level of approximately 25 to 30 mm. of mercury, whereas at a lower pressure these changes are unnoticeable.[36]

That the pulmonary veins in left ventricular failure behave in the same way as in mitral heart disease was shown by Lavender and co-workers.[28] Laminagraphy can be of considerable help in detecting these vascular changes so that pulmonary angiography is not always necessary.

The second feature which must be considered are the parenchymal changes due to pulmonary edema. These can be either intra-alveolar or interstitial. Acute intra-alveolar edema is characterised by confluent shadows in the lung fields, usually in the central areas, the so-called "butterfly shadows" or "batswing shadows."[8,24] These confluent shadows occur commonly bilaterally (Fig. 7) but they can be unilateral. They are not always confined to the bases or central areas of the lungs but can also affect the apices and posterior segments of the lungs. The mechanism for the distribution of the edema fluid is by no means certain, but deviation of blood from the lower

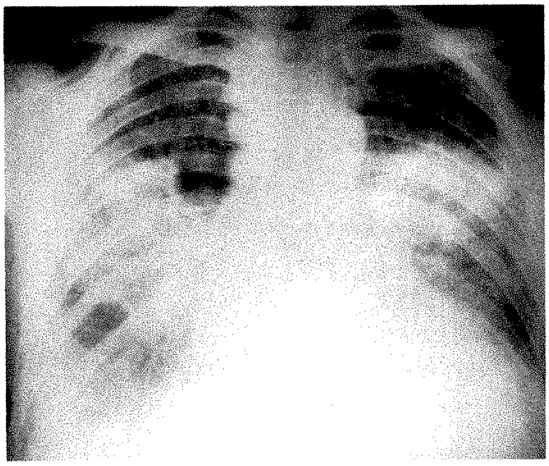

Fig. 7. Chest roentgenogram of a patient with systemic hypertension and acute left ventricular failure. There is evidence of widespread intra-alveolar pulmonary edema in both lungs (batswing shadows).

zones to the upper and mid-zones in patients with mitral heart disease and pulmonary arterial hypertension and in patients with left ventricular failure may be a contributing factor. Posture, too, may play a part when these patients suddenly develop left sided heart failure and thus edema fluid accumulates in the most dependent parts of the lungs.[36,37]

Interstitial pulmonary edema, often chronic, is much more common than intra-alveolar edema and occurs frequently in severe mitral stenosis and left sided heart failure, irrespective of the cause. The appearance of horizontal septal lines in the lungs is the characteristic roentgenologic finding. These septal lines are usually visible at the edges of the lungs in the lower and mid-zones (Fig. 8). Septal lines were first described by Kerley[27] and subsequently identified as due to a combination of shadows of distended interlobular pulmonary septa and dilated pulmonary lymphatics.[12,18,19,20,34] It has been shown that septal lines occur if the pulmonary capillary venous pressure is elevated above a level of about 25 mm. of mercury.[5,19,29] The appearance of septal lines may precede the clinical signs of pulmonary edema and thus provide the first indication of incipient left heart failure. With clinical improvement in the patient's condition and a decrease of the pulmonary venous pressure, septal lines can disappear very rapidly (Fig. 9, *A* and *B*).

Blurring of the pulmonary markings and lung fields, particularly at the bases and extending towards the root shadow of the lungs and also into the mid-zones, is due to accumulation of edema fluid (Fig. 10, *A* and *B*). It is this feature which makes interpretation of the pulmonary vascular pattern rather difficult, causing poor definition of the finer outlines of pulmonary arteries and veins. The clouding of the lung fields is entirely due to the accumulation of edema fluid in the interlobular septa, leaving the alveolar spaces clear.

As in the vascular studies of the lungs, correlation of the roentgenologic appearance with pathologic findings is very satisfactory (Fig. 11) and some of these points have been well described by many workers.[18,22,34] The pathological physiology of the

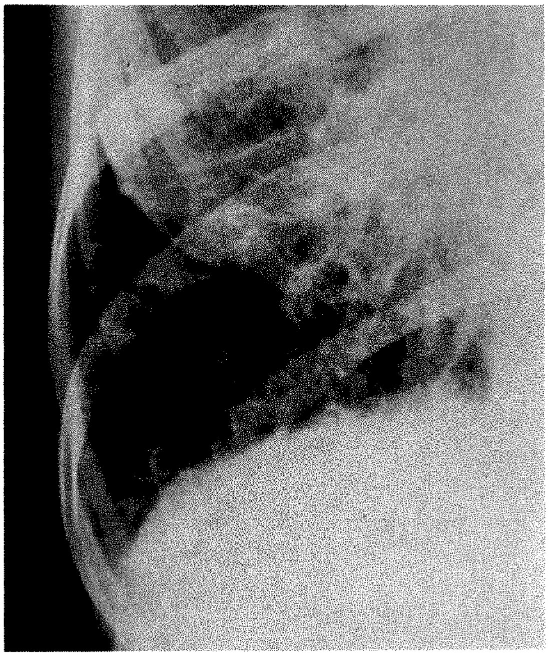

Fig. 8. Localized view of the right lower lobe of a patient with mitral heart disease and severe pulmonary hypertension. There is evidence of marked interstitial pulmonary edema with septal lines in the peripheral lung fields.

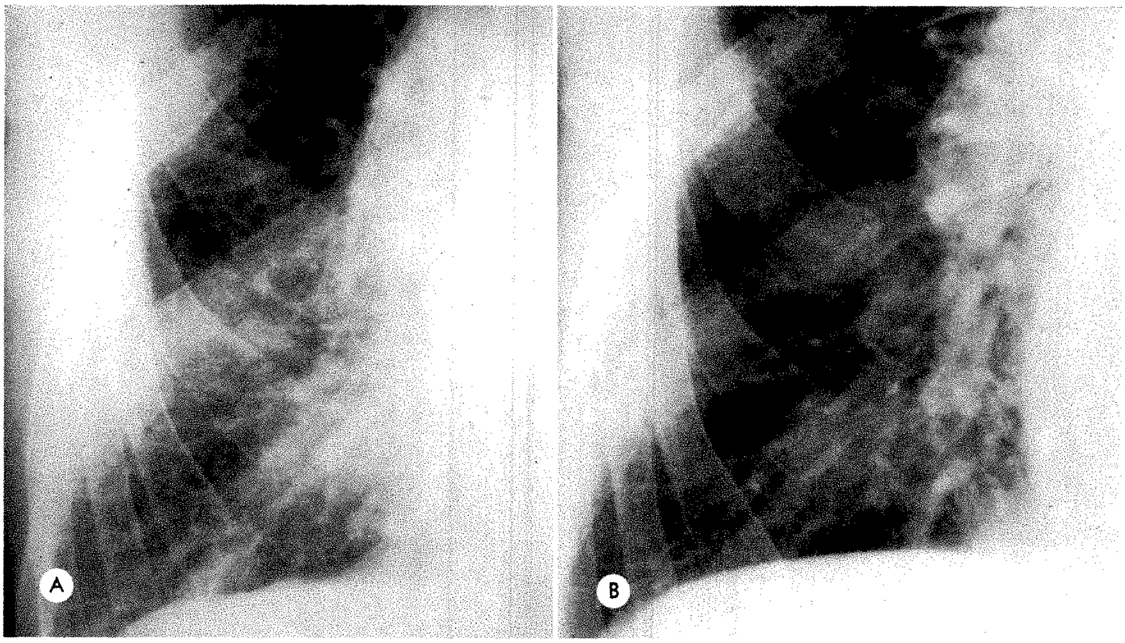

Fig. 9. (*A*) Localized view of the right lower lobe of a patient with left ventricular failure due to aortic valve disease. There is marked interstitial edema demonstrated by septal lines. (*B*) Same patient a day later. The septal lines have virtually disappeared.

pulmonary lymphatic flow in relationship to intra-alveolar and interstitial pulmonary edema is not too well known. In experimental studies of dogs, it has been shown by Rabin and Meyer[33] that lymph flow is not significantly increased in acute pul-

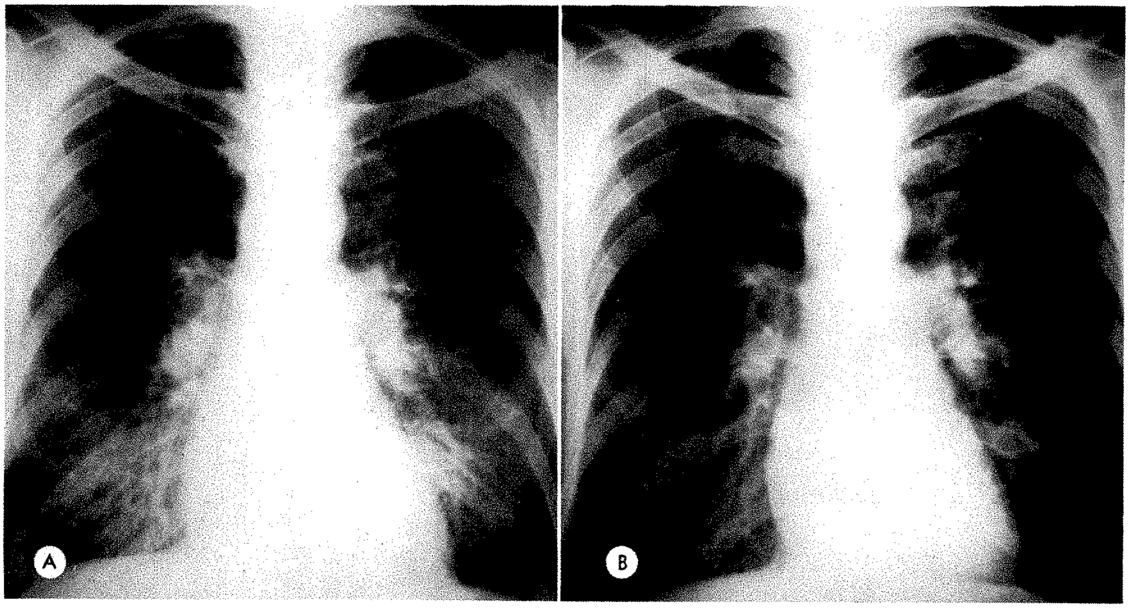

Fig. 10. (*A*) Chest roentgenogram of a patient with aortic valve disease and left ventricular failure. Note the severe interstitial pulmonary edema in the lower zones and the inadequate definition of pulmonary vascular markings due to this edema. (*B*) Same patient 2 days later after satisfactory treatment. The edema has completely cleared.

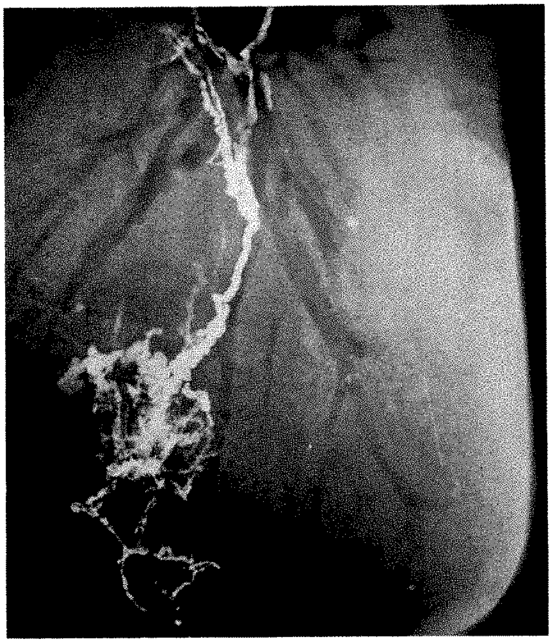

Fig. 11. Postmortem specimen of part of a lung of a patient who died with tight mitral stenosis and severe interstitial pulmonary edema. The surface lymphatics of the lung have been injected with contrast medium. Note the very distended surface lymphatics and the main draining lymphatics running peribronchially towards the root shadow.

monary edema with a left atrial pressure below 25 mm. of mercury systolic. When the left atrial pressure is elevated above this level, an appreciable change in the amount of lymph flow appears. This suggests that a functional relationship between interstitial pulmonary edema, elevation of the left atrial pressure, and thus of the pulmonary venous pressure exists. Some further anatomic studies of the pulmonary lymphatics, of their appearance and distribution in the human lungs, have recently been provided by Trapnell.[38]

Another important but rare cause of pulmonary venous hypertension is veno-occlusive disease. In some case reports which have been published, there was an association of pulmonary hypertension with various congenital abnormalities of the pulmonary veins, particularly of their insertions.[2,10,11] The roentgenologic findings of the lungs in pulmonary veno-occlusive disease are similar to those described above.

There is yet another cause for pulmonary venous hypertension which is of considerable roentgenologic and clinical interest. In some patients with mitral valve disease or left atrial myxoma, a persistent basal effusion is sometimes noted and this may be due to venous thrombosis or venous occlusion by tumor[37] (Fig. 12, *A* and *B*).

The recognition of roentgenologic signs of pulmonary venous hypertension is of great importance clinically, particularly in the diagnosis of patients with unexplained and unusual cardiac murmurs. These roentgenologic findings may point in the first instance to a diagnosis of an atrial tumor or veno-occlusive disease and are therefore the first pointers to a correct diagnosis.

The next problem to be discussed is the roentgenologic appearance of the lungs due to chronic pulmonary heart disease or "cor pulmonale." The most common condition in this group is chronic bronchitis, where the pulmonary vascular changes associated with pulmonary arterial hypertension are partly due to vasoconstriction mediated by hypoxia and partly due to some destruction of the lung parenchyma and therefore obliterative, probably mechanical vascular obliteration. It is not yet fully established which factors are mainly responsible for pulmonary hypertension in chronic bronchitis, but there is little doubt that hypoxia is probably the most important.

During the acute exacerbation of chronic bronchitis, considerable right sided cardiac enlargement will be seen on a plain chest roentgenogram. There will also be marked dilatation of the main pulmonary artery and main branches. This vascular dilatation may be so marked that the appearance may simulate a septal defect with an increased pulmonary blood flow. A further factor, which probably plays a part to explain the pulmonary hyperemia is the development of a secondary polycythemia, which by itself will lead to over-distention and overfilling of the smaller pulmonary vascular branches.[32] During the recovery phase, pulmonary vascular distention disappears

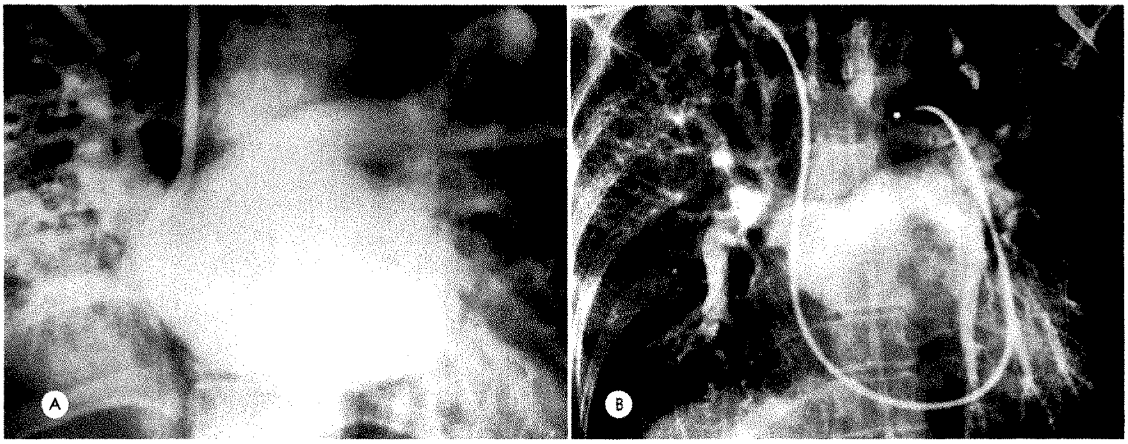

Fig. 12. (*A*) Right ventricular angiogram, pulmonary venous phase, of a patient with mitral heart disease and a persistent right pleural effusion. This demonstrates nonfilling of the right lower lobe and middle lobe veins. On the left side all pulmonary veins are demonstrated. The dilated atrium is free of thrombus. At mitral valvotomy the surgeon noticed blood clot at the origin of the right lower and middle lobe veins when he explored the atrium with his finger. (*B*) Anteroposterior angiocardiogram of a patient with a left atrial myxoma. The tumor is clearly demonstrated in the left atrium. Note good filling of the right upper and middle lobe veins. The right lower lobe veins have not filled. Contrast material is retained in the right lower lobe pulmonary artery and some of its branches, and the peripheral branches are tortuous and distended. On the left side both the upper and lower lobe veins are outlined and there is some contrast retention in the lower lobe arteries. At operation, it was noted that the myxoma had obstructed the right lower lobe veins.

rapidly and there is a marked diminution in size of the right ventricle and also decrease in size of the main pulmonary artery and branches. Persistence of cardiac enlargement with dilatation of the pulmonary arteries is an ominous sign, indicating severe irreversible right ventricular failure.

Some of the parenchymal diseases of the lungs associated with extensive fibrosis and advanced structural destruction of lung tissue, as for example progressive fibrocaseous chronic pulmonary tuberculosis, advanced pneumoconiosis, scleroderma, postirradiation pulmonary fibrosis or lymphangitis carcinomatosa, may all lead to the development of cor pulmonale, due to obliteration of the capillary network and also due to hypoxia. The appearance of the heart shadow and of the main pulmonary vascular pattern in these various disorders can be similar to that seen in chronic bronchitis, but in most instances will inevitably be overshadowed by the underlying lung disease.

Pulmonary arterial hypertension due to arterial obliteration is usually due to thromboembolic pulmonary vascular disease.[6,15] This disorder is of considerable roentgenologic importance since the diagnosis can sometimes be suspected from the plain chest roentgenogram before there is clinical evidence of such a diagnosis.

The roentgenologic appearance of thromboembolic pulmonary hypertension is best divided into two distinctive groups:

(1) Diffuse obliteration of the very small pulmonary arteries. In this group a marked discrepancy between the size of the main pulmonary artery and main branches, which may be considerably dilated, and narrowing of the very small peripheral branches, suggesting peripheral ischemia, can be seen.[6]

(2) There may be obstruction of the major arteries, or even thrombosis of the right or left main pulmonary artery. In this group a much more patchy ischemia in the peripheral lung fields associated with marked distention of the main arteries proximal to the obstruction will be notice-

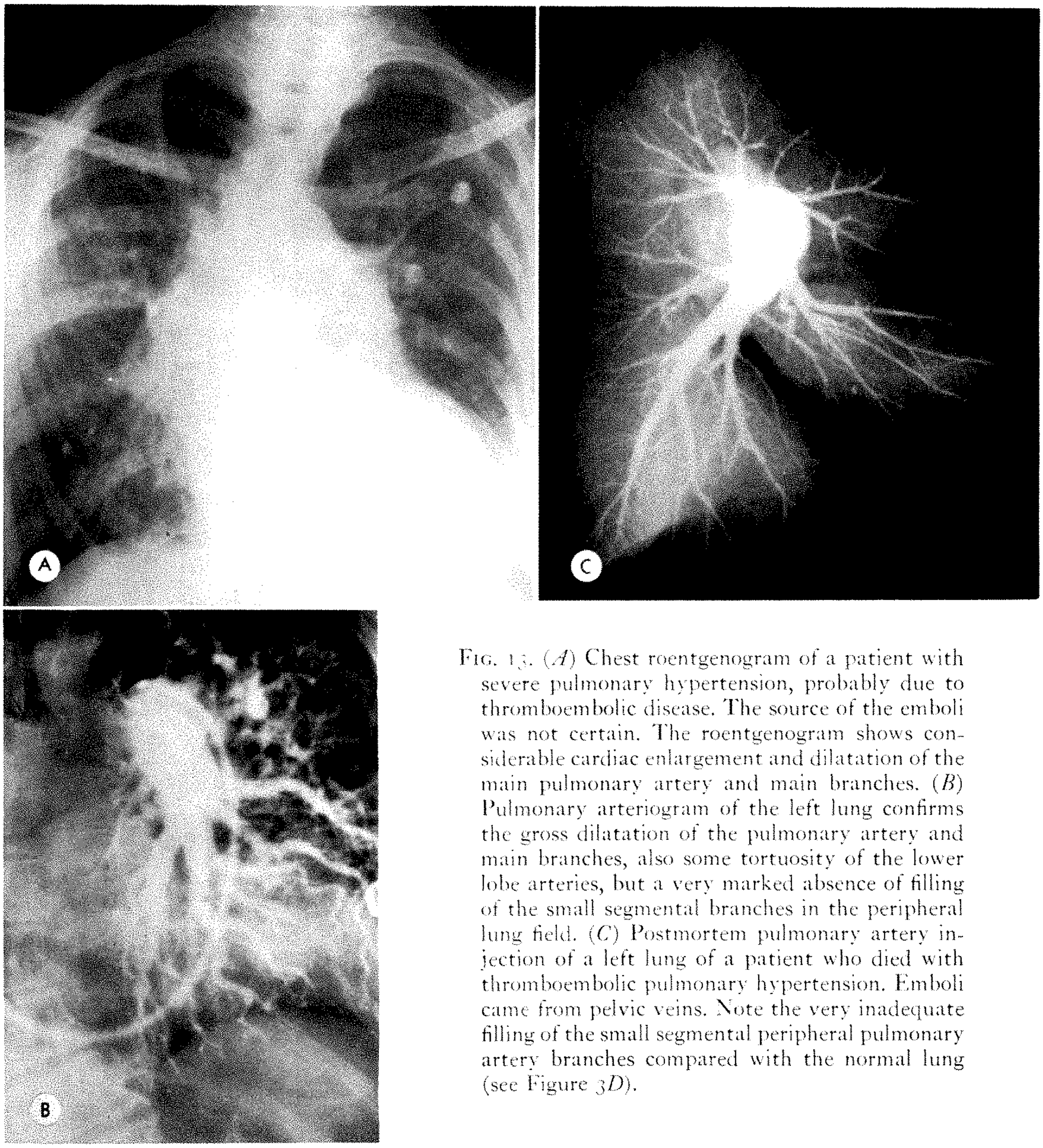

Fig. 13. (*A*) Chest roentgenogram of a patient with severe pulmonary hypertension, probably due to thromboembolic disease. The source of the emboli was not certain. The roentgenogram shows considerable cardiac enlargement and dilatation of the main pulmonary artery and main branches. (*B*) Pulmonary arteriogram of the left lung confirms the gross dilatation of the pulmonary artery and main branches, also some tortuosity of the lower lobe arteries, but a very marked absence of filling of the small segmental branches in the peripheral lung field. (*C*) Postmortem pulmonary artery injection of a left lung of a patient who died with thromboembolic pulmonary hypertension. Emboli came from pelvic veins. Note the very inadequate filling of the small segmental peripheral pulmonary artery branches compared with the normal lung (see Figure 3*D*).

able.[6,14] In a number of instances, however, the appearance on the plain chest roentgenogram can be very disappointing and occasionally even misleading. A detailed evaluation of the type of underlying pulmonary arterial obstruction is best obtained by pulmonary arteriography. This investigation will either demonstrate a very extensive peripheral obstruction with pruning and obliteration of the very small arteries due to small thrombi or emboli (Fig. 13, *A*, *B* and *C*) or there may be quite obvious main artery obstruction due to massive thrombosis[6] (Fig. 14, *A* and *B*). The source of emboli can be very varied; in some patients there is evidence of thrombophlebitis of the leg veins. Emboli may arise from thrombosis in pelvic or lumbar veins, but occasionally there is no apparent cause found even at postmortem examination.

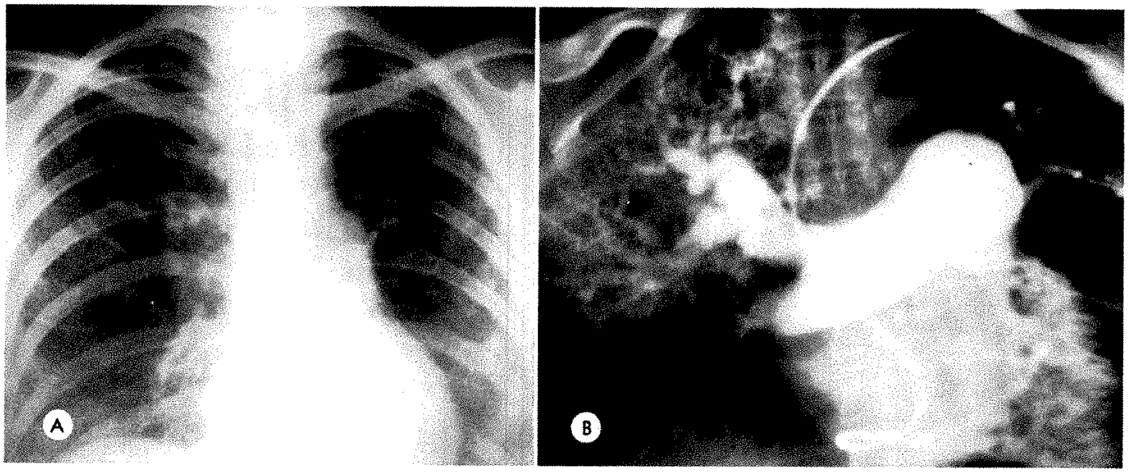

FIG. 14. (*A*) Chest roentgenogram of a patient with severe pulmonary hypertension following pregnancy. Note the dilatation of the main pulmonary artery and also of some of the right main branches and the relative ischemic areas in the left upper lobe. (*B*) Pulmonary arteriogram of the same patient. This demonstrates a patent right upper lobe artery. It appears that the greater part of the cardiac output flows through the right upper lobe. The right middle and lower lobe arteries do not fill and appear to be completely obstructed and so does the left lower lobe artery. There is only a minimal flow of contrast material through some of the left upper lobe arteries. Note the marked discrepancy between the appearance on plain roentgenograms and the angiocardiogram findings. Some of the vascular markings in the lower zones particularly are probably due to bronchial arteries.

Packed pulmonary emboli due to malignant disease, particularly trophoblastic tumors must be mentioned as yet another important source.[1] The disorder of thromboembolic pulmonary hypertension is of great interest in young patients, particularly in young females after parturition when repeated showers of pulmonary emboli probably arising from pelvic veins can obliterate the pulmonary vascular bed.

Frank pulmonary infarction is not a common feature of thromboembolic pulmonary hypertension[13] nor are there parenchymal shadows present in the lungs due to vaso-occlusion (Fig. 15, *A*, *B* and *C*). This is in contrast to vascular occlusion associated with various types of arteritis when pulmonary parenchymal shadows due to exudate or hemorrhage are quite frequent. As a sequel to extensive and progressive arterial occlusion, a bronchial artery pattern may become obvious on the plain chest roentgenogram.[6] In some cases of main artery thrombosis, vascular calcifications have been noted.[14]

Since an obvious source of pulmonary embolism is sometimes not evident, the differentiation between packed pulmonary embolism and primary pulmonary hypertension, a very rare disease indeed, may be difficult. It appears on histological grounds that the majority of cases which were labelled primary pulmonary hypertension, in fact, fall into the group of cases of packed pulmonary embolism or pulmonary artery thrombosis.[21,31] The term "primary pulmonary hypertension" must therefore be reserved for the small group of patients who show the persistence of the fetal type of pulmonary vasculature often associated with septal defects.[21] In these cases there is marked intimal thickening and muscular hypertrophy of the muscular pulmonary arteries from birth, resulting in partial obliteration and obstruction to blood flow with a high vascular resistance. The roentgenologic appearance of the lungs in this group of patients is very similar to that seen in patients with packed pulmonary embolism. There is evidence of right sided cardiac enlargement, dilatation of the main pulmonary artery and main branches with a

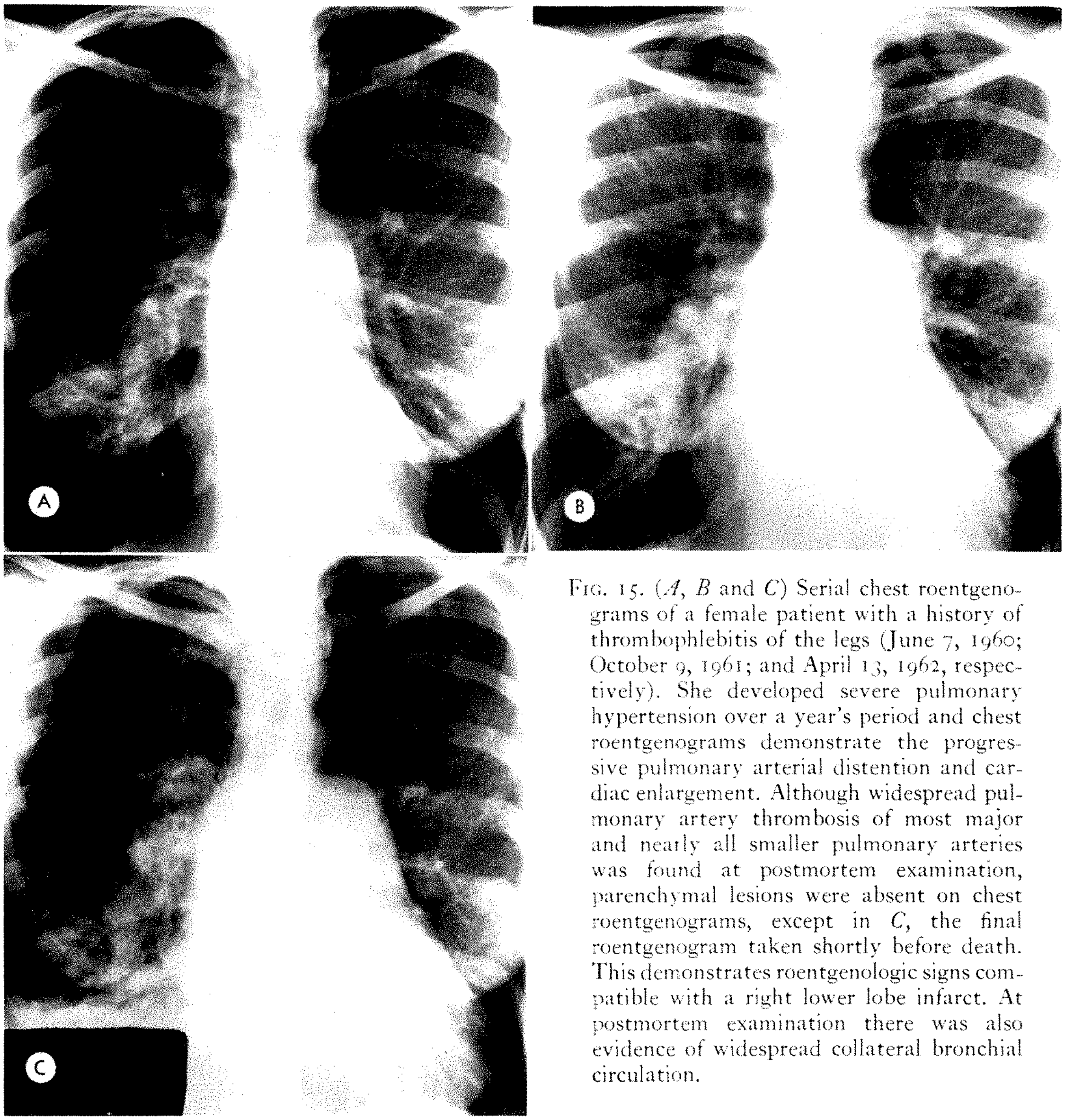

FIG. 15. (*A*, *B* and *C*) Serial chest roentgenograms of a female patient with a history of thrombophlebitis of the legs (June 7, 1960; October 9, 1961; and April 13, 1962, respectively). She developed severe pulmonary hypertension over a year's period and chest roentgenograms demonstrate the progressive pulmonary arterial distention and cardiac enlargement. Although widespread pulmonary artery thrombosis of most major and nearly all smaller pulmonary arteries was found at postmortem examination, parenchymal lesions were absent on chest roentgenograms, except in *C*, the final roentgenogram taken shortly before death. This demonstrates roentgenologic signs compatible with a right lower lobe infarct. At postmortem examination there was also evidence of widespread collateral bronchial circulation.

marked ischemia in the peripheral lung fields, and in most instances there may be evidence of an underlying congenital heart lesion, such as an atrial or ventricular septal defect.[6]

SUMMARY

I hope I have succeeded in demonstrating and explaining some of the roentgenological contributions to the study and understanding of pulmonary circulation.

These contributions should only be looked upon as a beginning and a stimulus for further endeavors to achieve even greater advances in the application of roentgenological methods in functional studies of the normal and pathological pulmonary circulation.

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UNILATERAL PULMONARY HYPOPLASIA IN AN ADULT*

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HYPOPLASIA of one lung is a congenital anomaly in which a more or less normally branching main bronchus is accompanied by underdeveloped alveolar tissue resulting in a small, nonfunctioning and fibrotic lung. The subject was exhaustively studied by Schneider[23] in 1913 and by Monaldi[16] in 1958. Schneider's classification has been widely accepted.[10,14,19] The defective development of the lung is present at birth, is usually unilateral and frequently is accompanied by malformations in other areas. It may, however, pass unnoticed until adulthood, is compatible with a full life span,[9] and may be a surprise finding at autopsy.[13] The roentgenographic appearance and the clinical course make unilateral pulmonary hypoplasia of the adult an entity different from pulmonary agenesis, aplasia and hypoplasia in children[4,8,9,12,15] while anatomically there is no clear-cut difference.[17]

Among the numerous cases of aplasia of one lung in an adult published in recent years, 14 can be considered and classified as hypoplasias rather than as complete aplasias. These 14 cases are: 2 of Rubio and Piovano,[22] 1 of Edwards,[6] 7 of Barna and Arvay,[1] 2 of Reventos *et al.*[20] and 2 of Roche and Chemin.[21] More could probably be added to this number, particularly among the cases reviewed by early writers like Mueller[17] and Schneider,[23] but this requires a very critical review of all their cases.

The case reported here is believed to be another example of unilateral pulmonary hypoplasia in an adult. In addition to the underdeveloped pulmonary parenchyma there is bronchiectasis. Such a combination has been reported only once in recent years[22] although in the older literature[17] reference is made to the association of pulmonary hypoplasia and pulmonary "cysts," the term cyst being interchangeably used for pulmonary cyst and cystic bronchiectasis.[11]

REPORT OF A CASE

A 52 year old Negro female was admitted to the University of Illinois Research and Educational Hospitals complaining of hemoptysis of approximately 4 months' duration, increasing in severity and associated with dull pain over the right precordium. She experienced a tight feeling of the chest which increased with exertion. The patient had been asymptomatic her entire life and there was no history of cough, dyspnea or dysphagia. About 25 years prior to the admission she was apparently treated for lues.

The physical findings were confined to the chest. The right side of the thorax seemed to be slightly contracted, however, with no significant narrowing of the intercostal spaces. There was dullness on percussion over the right chest and the breath sounds were distant. The heart sounds were shifted to the right but there were no murmurs. The blood pressure was 110/70. Laboratory data were within normal limits, except for the pulmonary function tests, which gave the following results: vital capacity 2.2 liters or 83 per cent of the normal; 1 second vital capacity 1.48 liters or 67 per cent of the normal; maximum breathing capacity 57 liters per minute, and air velocity index 0.89. Numerous sputum examinations for acid fast bacilli were negative, although one culture yielded chromogenic acid fast bacilli. However, the guinea pig inoculated with the culture died prematurely and the diagnosis of tuberculosis could neither be established nor ruled out.

The roentgenograms were most interesting. In the posteroanterior view (Fig. 1 *A*) there was a considerable shift of the mediastinum

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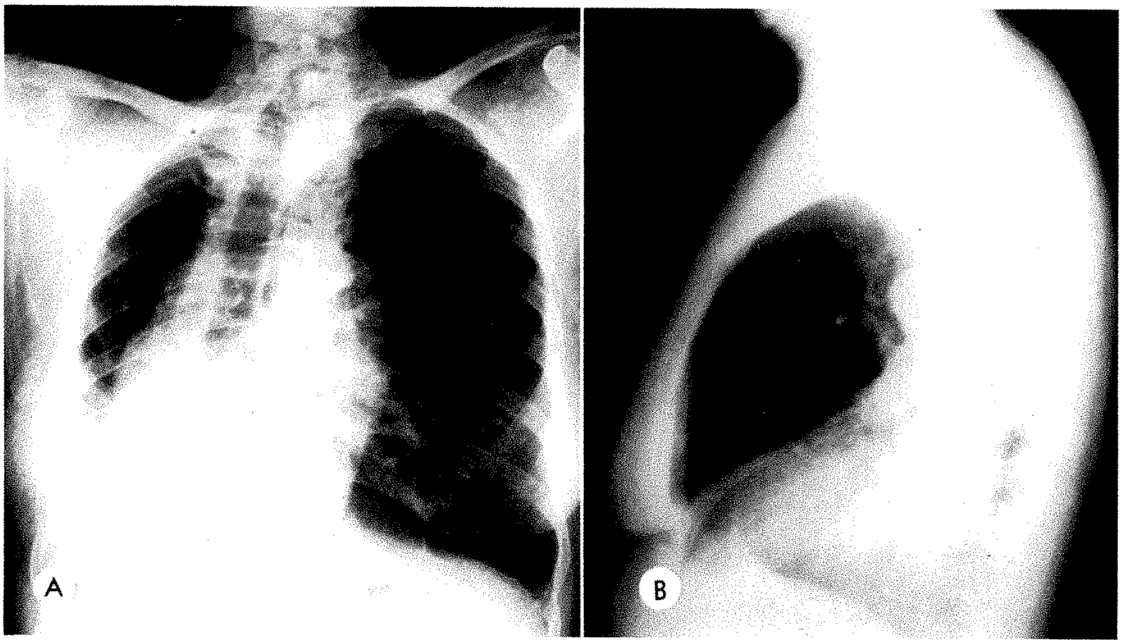

FIG. 1. (*A*) Posteroanterior and (*B*) lateral roentgenograms of the chest in an adult with unilateral right pulmonary hypoplasia. The mediastinal structures are displaced to the right and posteriorly. The left lung has herniated across the midline and has created the radiolucent area behind the sternum seen in the lateral view. The right lung has the appearance of a collapse but there is very little asymmetry of the thoracic cage.

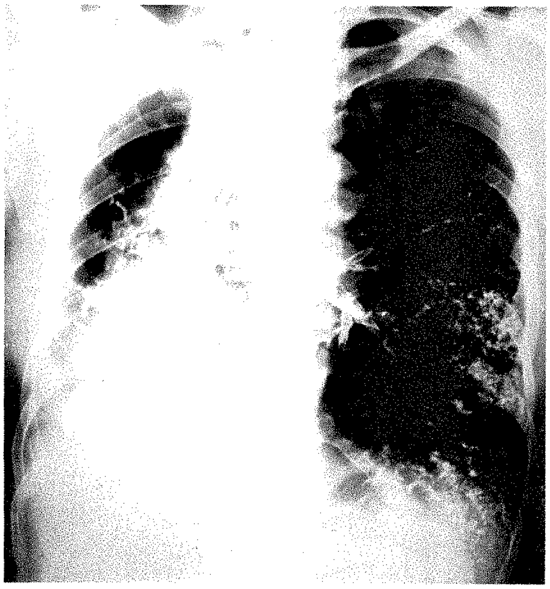

FIG. 2. Posteroanterior bronchogram of the chest. The right bronchi are crowded together and are dilated. The former suggests collapse, the latter bronchiectasis. There is alveolar filling on the left side but none on the involved side.

toward the affected right side. The right hemidiaphragm was elevated and the right costophrenic sinus was obliterated. The intercostal spaces were not significantly narrowed. There was a homogeneous density in the right lower lung field near the heart and close to the mediastinum. In the lateral view (Fig. 1 *B*) this density was seen as a triangular opacity overlying and posterior to the heart. The left lung was overaerated and there was herniation of the left lung across the mediastinum. The findings in general were not distinguishable from a collapsed right lower lobe except that the thoracic cage was relatively symmetric. A more careful examination of the right lower lung field showed multiple cystic structures similar to the ones seen in cystic bronchiectasis.

The bronchogram (Fig. 2) showed a marked shift of the trachea and the entire bronchial tree. The left bronchi were essentially normal, all branches were visualized and there was alveolar filling. Only some of the main branches were seen on the right side. They were crowded together, markedly dilated and ending with a convexity or sac-like structure (Fig. 3). No small branches or alveoli were filled. Judging from the bronchogram, it was concluded that the right lung was small or collapsed.

Bronchoscopy revealed a sharp carina with a marked shift to the right of the entire bronchial tree. The mucosa of the bronchi was normal throughout and no gross lesion was noted. It was concluded that the hemoptyses were due mainly to chronic, long-standing bronchiectasis and pneumonectomy was advised.

At surgery, the right chest was entered beneath the fifth rib and an entirely obliterated right pleural cavity was found. Working extrapleurally, the surgeon found bulging, functioning lung tissue, which actually represented left lung herniated across from left to right in the anterior mediastinum. The right lung was shrunken and functionless, although the bronchi entering the lung at the hilus were wide. The pulmonary artery and veins were small and in their proper places. The small, fibrotic right lung was removed in its entirety and postoperatively the patient did well.

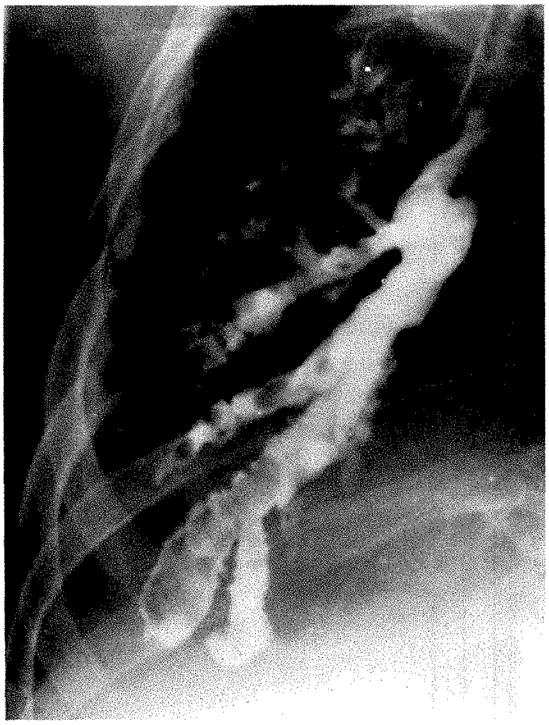

Fig. 3. Spot roentgenogram taken during bronchography. The whole right bronchial tree is fitted in one small roentgenogram. Filled are: the three upper lobe bronchi, one middle lobe bronchus and only two segmental bronchi from the lower lobe. The other three are just faintly visualized at their origin. All branches are dilated; the lower terminate with a sac-like structure, the upper with a cystic-like structure.

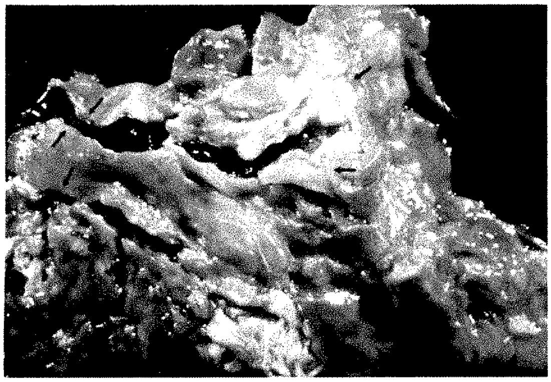

Fig. 4. Photograph of the entire right lung as removed at surgery. The actual measurements are 17×11×2 cm. The bronchi (left hand arrows) are filled with blood and are embedded in dense fibrous tissue containing no air (right hand arrows). The pleural surfaces are covered with shaggy fibrous adhesions.

The removed lung weighed 117 gm. and measured 17×11×2 cm. (Fig. 4). The external surface was dark red and covered with dense fibrous adhesive bands. The bronchi were large and dilated, the main bronchus measuring 2×1.5 cm. in diameter and 4.2 cm. in circumference. The dilatation of the bronchi extended to the periphery, where they were saccular and filled with dark red blood. All mucosal surfaces were gray, smooth and without ulcerations. The bronchi were surrounded by dark red, firm fibrous tissue, not recognizable as pulmonary parenchyma. There was no crepitancy. The blood vessels were small and grossly unremarkable.

Microscopically, the larger bronchi were lined with normal respiratory epithelium. The cartilaginous rings were well formed and showed occasional foci of ossification. The smaller bronchi were often distended by mucinous contents, but no terminal or respiratory bronchioles were seen. The bronchi contained mucous glands in their walls and numerous muscular bundles, revealing little or no chronic inflammation. The surrounding tissue was eminently fibrous, with large numbers of smooth muscle bundles, occasional mucous glands, and focal areas of slits varying in size, and lined by cuboidal epithelium in a single layer (Fig. 5). Occasional lymph follicles were present, as well as numerous eosinophils. No well-formed alveoli were found, the walls between the air spaces described above always containing generous amounts of fibrous tissue (Fig. 6); staining of elastic fibers failed to reveal the typical pulmonary pattern. The small arteries showed marked intimal proliferation with narrowing of the lumen. No anthracotic pigment was found. The diagnosis was extensive fibrosis of hypoplastic lung, probably congenital, with bronchiectasis.

DISCUSSION

The embryologic development of the bronchial tree and lungs is well documented in the literature.[2,3,5,8,16,17,23] Disturbances in the development of the bronchial tree occur at about the 26th to the 31st day of fetal age with the embryo measuring from 5 to 8 mm. Depending on the onset of the disturbance—the nature of which is not as yet understood—the bronchial bud will be absent entirely, rudimentary or more or less incompletely developed. Only with a fairly normal bronchial tree will the pulmonary parenchyma develop; otherwise, there will be only dense fibrous tissue. Monaldi[16] has explained the sequence of events and has divided the extent of the malformation into four degrees: first degree with no bifurcation of the trachea; second degree with a rudimentary main bronchus, no branching and a blind end; third degree with incomplete development after division of the main bronchus; and fourth degree with incomplete development of subseg-

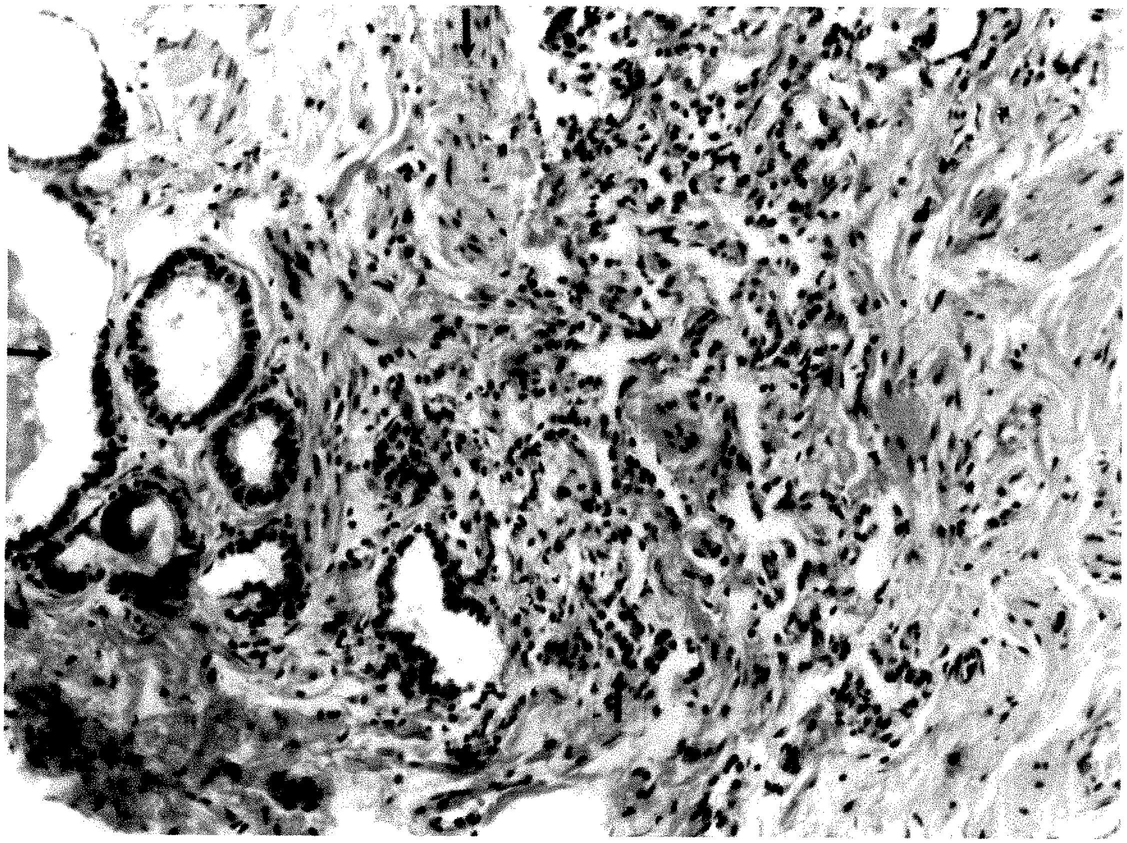

FIG. 5. Low-power photomicrograph of the hypoplastic lung. Dilated bronchial spaces (left arrow) lie within dense connective tissue rich in smooth muscle fibers (top arrow). Some secretions are present in the bronchial spaces but inflammatory changes are absent. Slit-like spaces resemble rudimentary alveoli (bottom arrow) but are functionless.

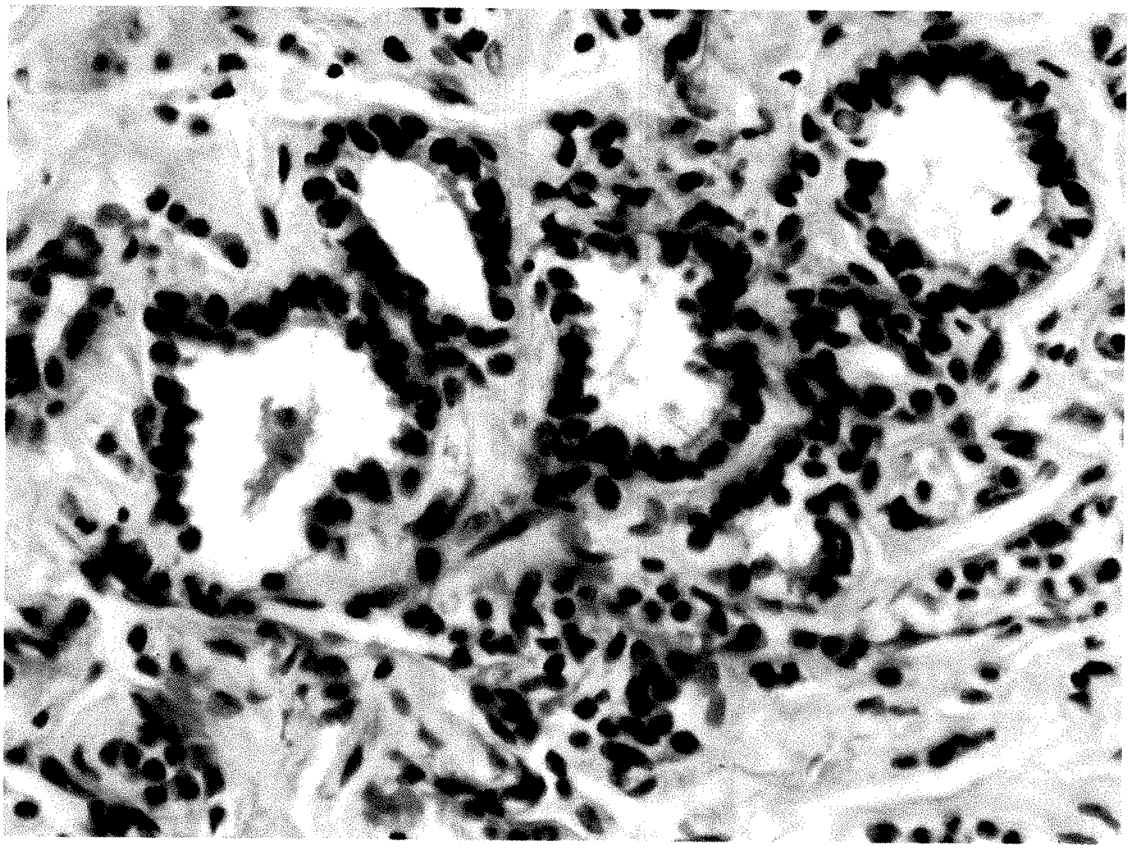

Fig. 6. High-power photomicrograph of another segment of the same lung showing parenchymal clefts lined with ciliated columnar epithelium secreting mucin. They are separated from each other by fibrous tissue containing collagen and smooth muscle fibers. Thin-walled alveoli are absent.

mental bronchi and small segments of the corresponding lobe. The case presented would fit into the third group of this classification.

In the original concept of Schneider,[23] pulmonary hypoplasia is associated with a small caliber main bronchus. This does not seem to be necessarily so; many reports mention bronchi of normal size and even with dilatation.[20,22] Since bronchiectasis and bronchogenic cysts may be associated with incomplete development of the pulmonary parenchyma,[17,22] the caliber of the bronchi seems to have little bearing on the degree of development of the distal lung as long as a minimum diameter is reached.

In contradistinction to hypoplasia in the infant, almost all cases of adult pulmonary hypoplasia were diagnosed incidentally. An acute pulmonary infection, hemoptysis or clinically manifest tuberculosis draw clinical attention to a lung which seems to be incompletely developed. At times a small, nonair-containing lung is discovered at autopsy unsuspectedly.

The clinical diagnosis is based on a triad suggested by Rubio and Piovano:[22] symmetric chest, great lateral displacement of the trachea and rotation of the mediastinum toward the affected side.

Although a long life span is possible with a hypoplastic lung, the poorly aerated and perhaps poorly nourished lung is susceptible to pyogenic infections,[1] tuberculosis with cavitation,[20,21] and hemoptysis.[1]

The treatment is surgical removal of the involved lung.[20,21,24]

ROENTGEN FEATURES

The roentgen diagnosis of adult pulmonary hypoplasia on the plain chest roentgenograms (Fig. 1, *A* and *B*) is believed to be difficult, particularly if there is an association with bronchiectasis; atelectasis with secondary bronchiectasis would give a similar roentgen appearance. An opacified tuberculous lung with bronchial stenosis can hardly be differentiated from a hypoplastic lung, and when the hypoplastic lung becomes involved by tuberculosis and has cavities, the roentgen diagnosis on plain roentgenograms is alsmot impossible.[20] According to Elward,[6] the features of pulmonary hypoplasia simulate the following conditions: croupous pneumonia of an entire lung, unilateral tuberculosis with fibrosis and pleural thickening, and unilateral pleural effusion with a fixed mediastinum.

The most striking features on the plain chest roentgenograms remain the marked shift of the mediastinum to the affected side, the absence or very minimal narrowing of the intercostal spaces and the herniation of the opposite lung across the mediastinum. The occurrence of an asymmetry of the thorax in congenital hypoplasia is prevented by expansion of the opposite lung immediately after birth and its herniation across the mediastinum. In acquired collapse of a lung, there is always a narrowing of the intercostal spaces.

When bronchiectasis is combined with hypoplasia, small cystic-like structures are noted near or over the dense small lung shadow (Fig. 1, *A* and *B*).

The diagnostic procedure of choice is bronchography.[5,8,9,21] Once the tracheobronchial tree has filled with contrast material, the diagnosis is imminent (Fig. 2). The entire bronchial tree is shifted to one side and there is no filling of small bronchi and alveoli. The visualized segments are usually the main bronchus only or the main bronchus and a few branches. The main bronchus can be short and narrow,[22] of normal size or ectatic.[22] If they are dilated, the bronchi terminate with a convexity or a cyst-like structure (Fig. 3). In an intrinsic bronchial lesion this end would be concave, and a sharply cut off crescent-like end is seen in an extrinsic lesion.[5]

Angiography is a procedure of value particularly if surgery is contemplated. The size, shape and position of the pulmonary artery and veins can thus be determined.[12] With defective development of the lung there may be an associated abnormal vascular supply leading to complication of the syndrome and, possibly, to difficulties in the surgical removal.[12,18]

PATHOLOGY

Pathologically, the picture may be varied. Characteristically, the bronchial structures appear relatively normal. Not infrequently, the cartilaginous rings form complete circles with absent pars membranacea. Their caliber may vary from below normal to much above normal, giving rise to the diagnosis of "bronchiectasis."[11] It may be impossible to determine if these bronchi, perhaps showing some chronic inflammation, were wide originally, or if they became wide as the consequence of inflammation. Since the lung does not function, the former appears somewhat more likely. The lining epithelium is usually normal and the mucous glands may not be unusual. There may be, however, any degree of variation in the development, quantity and relationships of these components. In our case for instance the amount of smooth muscle is increased rather out of proportion.

The branching of the bronchi may be quite variable, which fact is used by some as a criterion for classification.[16] When the main bronchus does divide, the extent of subdivision may range from rudimentary secondary bronchi to fairly complete respiratory bronchioles. In our case terminal bronchioles are absent but secondary and tertiary bronchi are fairly well formed.

Alveoli may be altogether absent or they may be rudimentary. The fibrous tissue around the existing bronchi may be so dense as to lack any clefts reminiscent of alveoli. Our case, with slits lined by cuboidal epithelium in a single layer, is rather more typical, with abundant fibroconnective tissue separating them. The epithelium is similar to that adjoining an area of chronic inflammation in a fully developed lung.

The vascularity of a hypoplastic lung again may vary from fairly dense tissue with relatively inconspicuous blood vessels, to very vascular, almost spongy parenchyma. The key feature is the connective tissue barrier between the small vascular channels and the air spaces, which makes gaseous exchange of any significance impossible. The main vessels may be normal or on occasion abnormal.[18] Marked arteriosclerotic narrowing, with or without pulmonary hypertension may be secondary. According to Ellis,[7] a vascular malformation is the etiologic factor determining pulmonary hypoplasia.

The differential diagnosis between a lung hypoplastic at birth due to a developmental defect and a lung severely scarred and nonfunctioning as the consequence of chronic inflammation may, on occasion, be difficult. In the absence of extensive scarring and anthracotic pigment, however, and with only relatively mild chronic inflammatory changes, the arrested development is clearly recognizable.

CONCLUSION

Pulmonary hypoplasia is a rare congenital anomaly sometimes discovered late in life. Fourteen adult cases have been reported in the literature thus far. An additional case of adult pulmonary hypoplasia with bronchiectasis is presented. The roentgen appearance of the chest is rather typical and consists of a relatively symmetric thorax, a considerable shift of the mediastinum toward the affected side and herniation of the opposite lung. Bronchography and pulmonary angiography are valuable procedures to establish the roentgen diagnosis. Anatomically, there is no primary difference between pulmonary hypoplasia in the adult and that in the child. The reason for detection in children is early infection, which is usually not as severe in cases discovered in adults. Surgical removal of the physiologically useless organ is the treatment of choice.

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BRONCHOGENIC CYST*

A REVIEW OF 46 CASES

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BRONCHOGENIC cysts are congenital lesions which are derived from the primitive foregut and usually found within the lungs or mediastinum. A review of the pathologically confirmed cases of bronchogenic cyst encountered at Fitzsimons General Hospital between the years 1946 and 1961 was undertaken in order to more firmly establish roentgenographic criteria for this entity. The roentgenograms of 46 cases were available and these form the basis for the present report.

HISTORICAL REVIEW

It is generally agreed[34,51,57] that Bartholinus described the first case of "cystic disease of the lung" in 1687. This was a cyst of the left upper lobe in a 4 year old male. Koontz[34] must be given credit for the stimulation of American interest in congenital cystic disease of the lung. He reviewed this topic in 1925, tabulating 108 cases without finding a single case in the American literature. Since that time many reviews have appeared, notably those of Schenck,[56,57] Sellors,[58] Pugh,[51] Maier,[41] and Conway.[16]

Bracher and Koontz[13] state in their publication that Meyer reported the first case of bronchogenic cyst of the mediastinum in 1859; however, Hare (according to Adams and Thornton[1]) found none in a review of 600 cases of mediastinal tumors reported prior to 1899. Chiari (according to Sowerbutts[60]) described 5 cases in 1899, Laipply[35] was able to collect 36 in 1945, and Bracher and Koontz[13] stated that slightly under 100 cases were reported prior to 1952. Numerous reports have appeared since that time.[6,7,8,13,19,21,26,60]

EMBRYOLOGY

The respiratory tract and esophagus have a common origin from the primitive foregut. A lateral septum invades from each side, forming a ventral and dorsal component, the former fashioning the tracheal bud and the latter the esophagus after their eventual separation.

Bronchogenic cysts are formed from an abnormal budding of the tracheal primordium or abnormal branching of the tracheobronchial tree.[35,40] The exact time of these events has not been ascertained but it might be assumed that intrapulmonary cysts are a result of rather late abnormal branching, whereas the abnormal budding which forms cysts found about the carina and trachea occurs somewhat earlier. Those cysts in association with the esophagus are formed still earlier. The latter might also originate from imperfect formation of the lateral invaginating septum.

Several cystic lesions with gross and microscopic characteristics of bronchogenic cyst have been reported which are not associated with either the trachea, bronchi, lungs, or esophagus. These lesions usually occur in a paraspinal location in the posterior mediastinum but have been found within the presternal soft tissues,[43,59] pancreas,[43] thoracic inlet,[47] and lower cervical region.[47] To date, it has been presumed that they are formed by complete separation of the abnormal bud and migration in the embryo to these locations. This remains conjectural.

The buds, because of their derivation, are lined by secretory epithelium. If the connection with the tracheobronchial tree is lost, the bud is distended and a cyst is formed by the secretions of the epithelium, whereas if a patent connection remains between the two the bud fills with secretions and is distended by them as well as by air following birth and the onset of respirations. The cyst, therefore, varies from being completely filled with fluid to complete filling by air, depending upon the degree of bronchial communication and the secretory capacity of the lining epithelium.

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This material has been reviewed by the Office of The Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any indorsement of the opinions advanced or any recommendation of such products as may be named.

PATHOLOGIC ANATOMY

Grossly, the bronchogenic cyst is a single, spherical, cystic mass possessing a thin wall and containing either air and/or a clear, serous, or thick, dark, mucoid material. When dark, mucoid material is present within the cyst, it is usually attributed to old hemorrhage. The cyst may, on section, be trabeculated or may contain multiple thin septa and, therefore, be multilocular.

Microscopically, the cysts contain one or more of the tissues that are normally found in the trachea or bronchi. Characteristically, they are lined with ciliated pseudostratified columnar epithelium. In portions of the cyst, squamous metaplasia may occur or the cilia and even the epithelium may be absent. The walls of the cyst consist of fibrous connective tissue which commonly, but not necessarily, contains glands, hyaline cartilage, smooth muscle, elastic fibers, and nerve trunks, either alone or in varying combinations.[35,38] When infection has occurred, the lining epithelium, as well as other characteristic tissues may be destroyed, making histologic verification difficult if not impossible. The absence of anthracotic pigmentation in the cyst wall has been proposed as proof of congenital origin and has been used by some in differentiating bronchogenic from acquired cysts.[36,56,58] This conclusion is disputed by Conway[16] and others. On occasion, in the presence of chronic infection, microscopic calcification may be present; however, the authors were unable to find a report of a pathologically verified bronchogenic cyst which displayed gross or roentgenographically apparent calcification. Maier[40] alone states that such calcification may occur although none was present in his series.

Womach and Graham[65] described epithelial hyperplasia in congenital cystic disease of the lung. In 1947 Moersch and Clagett[45] reported 2 cases of carcinoma arising in bronchogenic cysts, one an adenocarcinoma in a mediastinal cyst and the other a squamous cell carcinoma in a pulmonary location. Since that time, there have been reports in the English literature of 4 cases of squamous cell carcinomas[8,37,48,62] and a fibrosarcoma[9] arising in pulmonary bronchogenic cysts.

SYMPTOMATOLOGY

In general, the patient with a pulmonary bronchogenic cyst will fall into one of four categories: (1) those with signs and symptoms of a pulmonary infection; (2) unexplained hemoptysis; (3) dyspnea, and cyanosis; and (4) symptom free, with an abnormal chest roentgenogram.

A high proportion of pulmonary bronchogenic cysts have a patent bronchial communication. Usually this communication is small, creating a stagnant pool of secretions behind it, which serves as an excellent bacterial culture medium; therefore, secondary suppurative infections within these cysts are frequent, being associated with cough, chest pain, and fever.

Hemorrhage into the cyst, even in the absence of infection, is not uncommon as is demonstrated by the frequent finding of dark, mucoid contents within them which represent the residuals of old hemorrhage. If a bronchial communication is present, hemoptysis may occur.

In the newborn period and during infancy, the patient commonly presents with dyspnea and cyanosis. This is created by a ball-valve mechanism at the bronchial communication, leading to air trapping, distention of the cyst, compression of adjacent lung tissue, and displacement of the mediastinal contents. There is no apparent explanation as to why this does not occur in later years.

Occasionally, dyspnea or wheezing is caused by a mediastinal bronchogenic cyst which compresses and narrows the lumen of the trachea or major bronchi. Similarly, dysphagia may be associated with esophageal compression.

In the absence of a bronchial communication symptoms are much less frequent. This is borne out by their relative paucity in the mediastinal group where the great majority is discovered on routine chest roentgenograms. A mediastinal bronchogenic cyst with a patent bronchial communication is rare.

PRESENT SERIES

This series of 46 cases was divided into 32 pulmonary and 14 mediastinal cysts and each group will be discussed separately as they presented different clinical and roentgenographic characteristics. The average patient age at the time of thoracotomy for the entire series was 24 years, the range being from 14 months to 48 years; 80.4 per cent of the patients were males. The sex distribution of the series is undoubtedly a reflection of the military population which this series represents, since in the literature, in general, an approximately equal sex ncidence is reported.

PULMONARY CYSTS

The average age in this group was 26.8 years, the range being from 2 to 48 years. Symptoms averaging 17 months in duration were present in 26 of the 32 patients (81.25 per cent). As seen in Table I, the most common were cough and chest pain. Hemoptysis was present in 8 cases and in 4 was the only symptom.

Table I

SYMPTOMS IN 26 OF 32 PATIENTS (81.25 PER CENT) WITH PULMONARY BRONCHOGENIC CYST

Cough	16
Chest Pain	9
Hemoptysis	8
Shortness of Breath	4
Fever	3

The general roentgenographic characteristics of a pulmonary bronchogenic cyst are a sharply defined, solitary, noncalcified round or oval density confined to a single lobe, usually a lower lobe, which changes little in size over a long period of time. The cyst will present in one of three categories: (1) that of homogeneous water density (Fig. 1, *A* and *B*); (2) an air filled cyst; and (3) a cyst containing an air fluid level (Fig. 2, *A* and *B*). The walls of the latter two are very thin, usually measuring 1 to 2 mm. and fine septa may be seen crossing through the cyst (Fig. 3, *A* and *B*). During the period of observation, a cyst may vary in any of the three categories. There is little, if any, evidence of surrounding inflammation. In this series, 8 cysts were oval in shape, 18 spherical, and 6 were somewhat irregular or lobulated. The smallest cyst measured 1.0×2.0×2.0 cm. and the largest 9.0×10.0×11.0 cm., the mean dimension being 4.0×4.0×6.5 cm. Fifteen were found in the right lung and 17 in the left. Twenty-one (65.6 per cent) were located in the lower lobes, 10 in the right, and 11 in the left (Table II). The lobar distribution of the remainder is also given in Table II. Four cysts were in close association with the hilar vessels and could not be separated from them roentgenographically but at surgery were found to lie within the pulmonary parenchyma. Twelve cases presented as air filled cysts, 9 of which subsequently developed an air fluid level. Seven cases presented with an air fluid level and 13 cases initially presented

Table II

LOCATION OF PULMONARY BRONCHOGENIC CYST

Lobe	Lung		Total	
	Right	Left	No.	Per Cent
Upper	3	6	9	28.1
Middle	2	—	2	6.3
Lower	10	11	21	65.6
Total	15	17	32	100.0

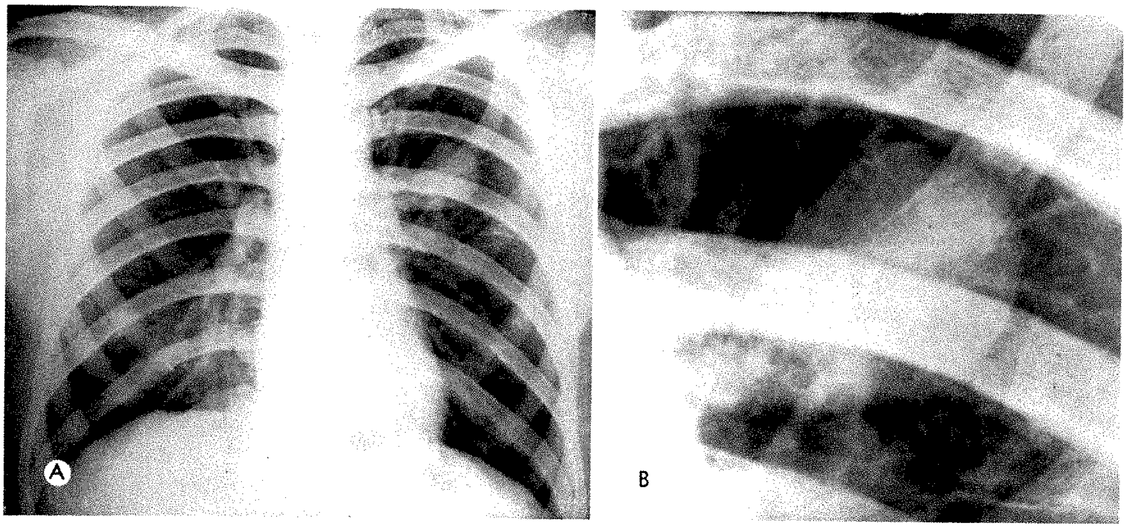

Fig. 1. (*A* and *B*) A 24 year old white male with a short history of productive cough was followed for 4 years with roentgenographic evidence of a small mass lesion in the superior segment of the left lower lobe which increased in size from 1.5×2.5 cm. to 4.0×4.0 cm. Surgical removal confirmed the diagnosis of a bronchogenic cyst.

as a homogeneous water density, 4 of which developed an air fluid level. During the course of observation, 20 (62.5 per cent) demonstrated an air fluid level (Table III).

None of the cysts showed roentgenographic evidence of calcification although microscopic evidence was found in 2 specimens.

Bronchograms in 18 of the 32 cases were available for interpretation: One-third, or 6, revealed bronchographic medium within the cyst. In 2 studies bronchiectasis was noted in the same lobe as the cyst; in neither was this abnormality noted elsewhere. The remainder showed only bronchial displacement in the region of the cyst.

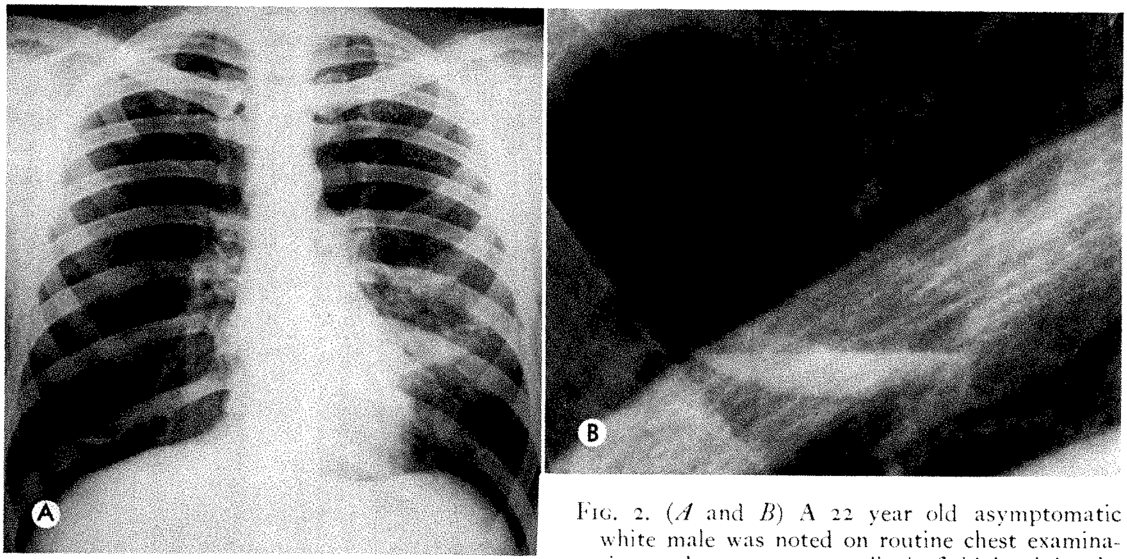

Fig. 2. (*A* and *B*) A 22 year old asymptomatic white male was noted on routine chest examination to have a very small air fluid level in the right lower lobe. Bronchographic examination did not result in contrast material entering this region. Operative removal confirmed the presence of a very thin-walled bronchogenic cyst.

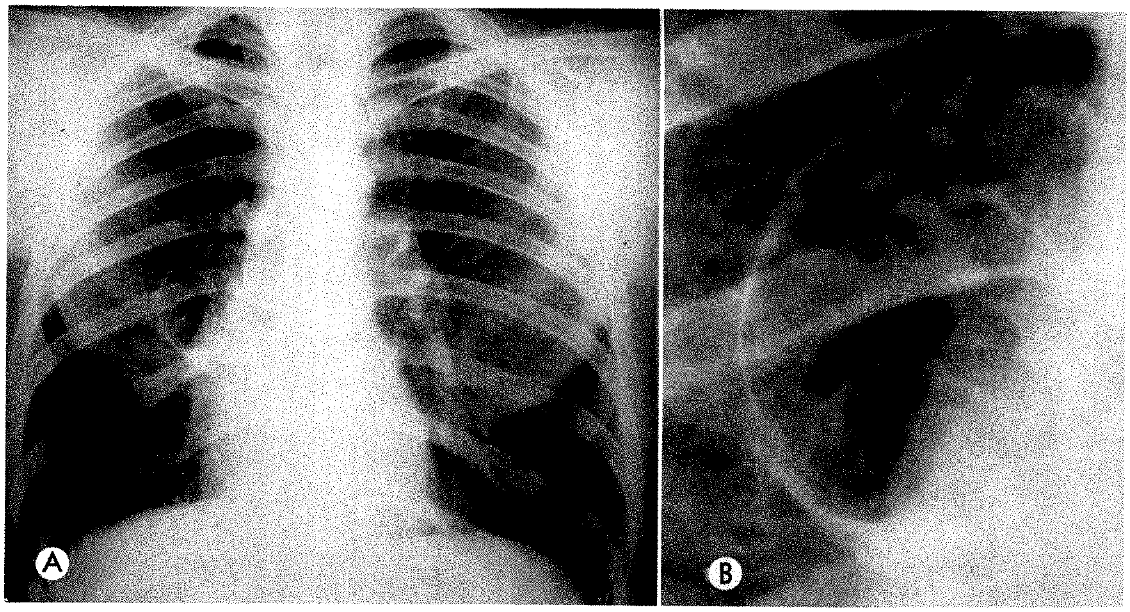

Fig. 3. (*A* and *B*) A 25 year old white male presented symptoms of intermittent nonproductive cough for 9 months. Chest roentgenograms revealed a thin-walled septated cystic structure adjacent to the right hilar area. Bronchograms revealed bronchial communication. Surgical removal resulted in the pathologic diagnosis of bronchogenic cyst.

In no case did medium enter a cyst of solid water density.

MEDIASTINAL BRONCHOGENIC CYST

The average age in the group was 20.9 years; the range being from 14 months to 28 years. Nine (64.3 per cent) of the 14 cysts were discovered on routine chest roentgenograms. Symptoms were present in 5 (35.7 per cent) of the 14 patients and were of a mild and intermittent nature in each case. They consisted of occasional nonproductive cough, chest discomfort or pain, and shortness of breath. No patient in this group experienced hemoptysis.

The accepted roentgenographic characteristics of a mediastinal bronchogenic cyst are a homogeneous, smooth, solitary, round or ovoid, noncalcified mass located in the middle, posterior, or superior mediastinum in close association with the trachea or major bronchi. The most typical lesion is that which arises from the inferior aspect of the carina (Fig. 4) and extends inferiorly. Attachment to the trachea and major bronchi is common and this may be demonstrated at fluoroscopy by motion of the mass in association with the trachea during the act of swallowing. A patent communication between a mediastinal bronchogenic cyst and the tracheobronchial tree must be considered a rarity as the authors were able to find, in their review of the literature, only 4 mediastinal bronchogenic cysts[1,14,31,43] which presented with an air fluid level. All 4 were in a subcarinal location.

Table III

AIR FLUID LEVEL FORMATION IN PULMONARY BRONCHOGENIC CYST

	Presenting Category		Air Fluid Level Demonstrated	
	No.	Per Cent	No.	Per Cent
Air Filled	12	37.5	9	75.0
Air Fluid Level	7	21.9	7	100.0
Homogeneous Water Density	13	40.6	4	30.8
Total	32	100.0	20 or 62.5% of Group	

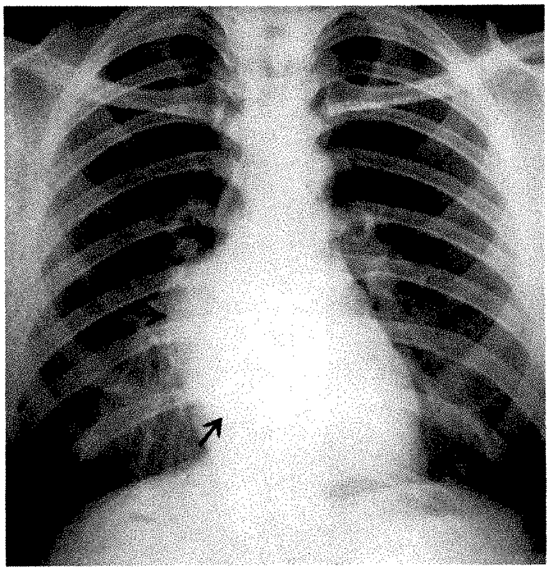

FIG. 4. A 25 year old asymptomatic Negro male demonstrated on a routine chest roentgenogram a large subcarinal mass which was found to displace the esophagus slightly to the left. This is the more typical characteristic of a mediastinal bronchogenic cyst. This diagnosis was confirmed by surgery and pathologic examination.

Because of their location, these cysts will commonly displace the esophagus. The deformity will usually appear as a smooth extrinsic defect; however, they may arise within the walls of the eosphagus and present as an intramural extramucosal mass.[14,43,54]

Fourteen (30.5 per cent) of the 46 bronchogenic cysts in this series were located within the mediastinum, 12 of which were ovoid in shape and 2 spherical. The smallest measured 3.0×3.0×2.0 cm. and the largest 10.0×7.0×6.0 cm., the mean dimensions being 5.0×6.0×3.5 cm., approximating closely the mean of the pulmonary group. Seven (50 per cent) were found within the posterior mediastinum (Fig. 5 and 6, *A* and *B*) and 5 (35.7 per cent) in the middle mediastinum, 4 of which were in a subcarinal location. Two (14.3 per cent) were in the superior mediastinum (Fig. 7, *A* and *B*), both of which were in a right paratracheal location (Table IV). The esophagrams were available for interpretation in 8 cases. Two of the studies were within normal limits, while the remaining 6 showed evidence of esophageal displacement. All 6 were caused by cysts arising either in a subcarinal location or within the posterior mediastinum and all were displacements to the left, 5 of which also had slight posterior displacement and one anterior. There were no cases of an intramural esophageal bronchogenic cyst.

TABLE IV

LOCATION OF MEDIASTINAL BRONCHOGENIC CYST

Mediastinal Compartment	Projection to		Subcarinal	Total	
	Right	Left		No.	Per Cent
Superior	2	0	—	2	14.3
Middle	1	0	4	5	35.7
Posterior	3	4	—	7	50.0
Anterior	0	0	—	0	0.0
Total	6	4	4	14	100.0

No case revealed either roentgenographic or microscopic evidence of calcification, nor did any cyst ever show evidence of an air fluid level.

DISCUSSION

Ordinarily routine roentgenograms, supplemented by fluoroscopy, are sufficient to

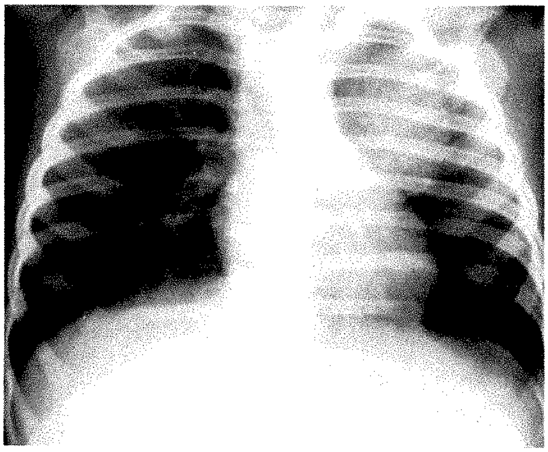

FIG. 5. A 14 month old asymptomatic white female on a routine chest roentgenogram presented a left posterior mediastinal mass pressing laterally into the region of the left upper lobe. Surgical removal confirmed the diagnosis of bronchogenic cyst.

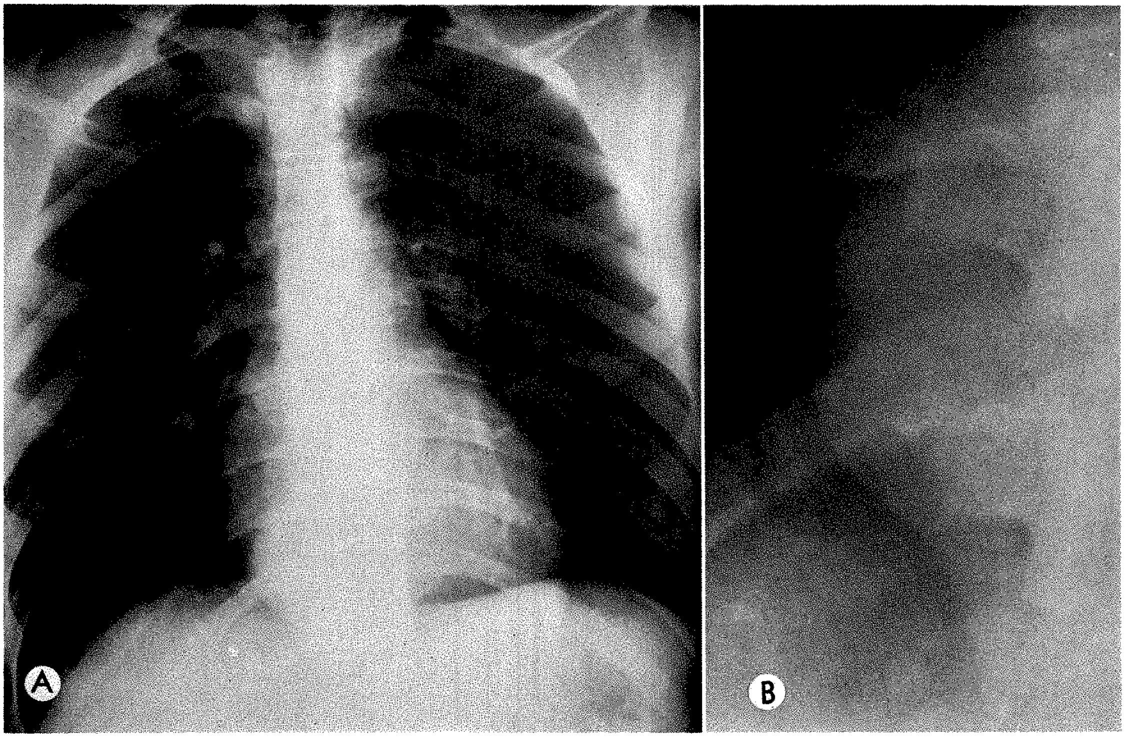

Fig. 6. (*A* and *B*) An 18 year old asymptomatic white male was noted to have a small posterior mediastinal mass on a routine chest roentgenogram. The preoperative diagnosis was a neurogenic tumor. At surgery, an extrapulmonary posterior mediastinal bronchogenic cyst was removed.

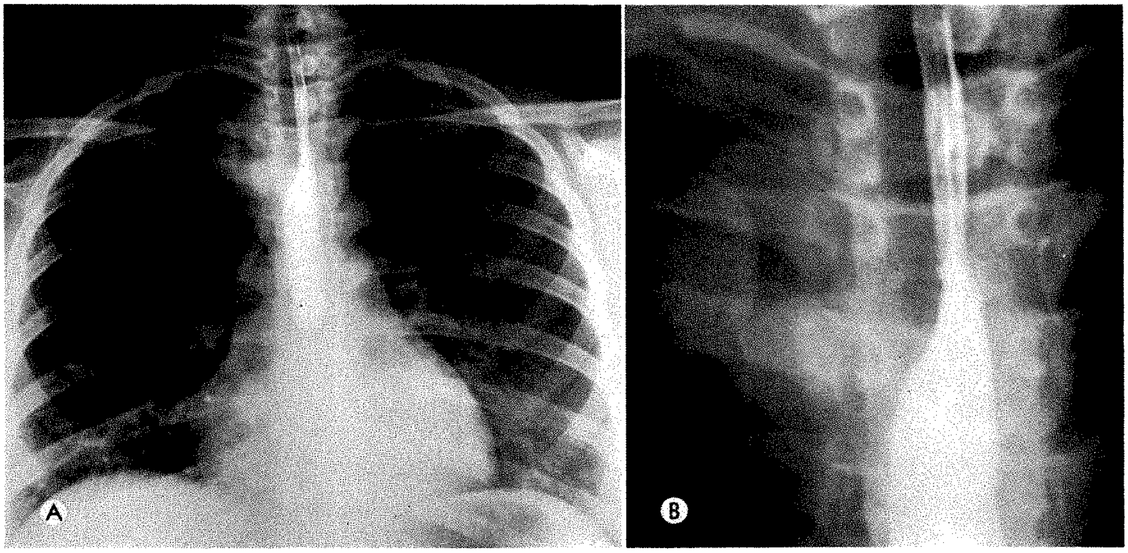

Fig. 7. (*A* and *B*) A 25 year old white female presented questionable symptoms of shortness of breath and dysphagia. Chest roentgenogram showed a right paratracheal superior mediastinal mass which was diagnosed as a bronchogenic cyst and proven at surgery.

make the diagnosis. Laminagraphy and roentgenograms obtained with a Potter-Bucky grid are sometimes of value in further defining the lesion, particularly when located in the subcarinal area or posterior mediastinum. Bronchograms, while adding little to the differential diagnosis, are helpful in localization and on infrequent occasions will demonstrate associated bronchiectasis. Angiography may be necessary to rule out vascular abnormalities.

Pulmonary bronchogenic cyst of homogeneous water density would have to be differentiated from benign and malignant tumors, as well as granulomas. Hamartomas are frequently calcified, whereas primary carcinomas are not sharply defined and will show increase in size over a rather short period of observation. Metastatic nodules are usually multiple. Granulomas are generally smaller, located in the upper lobes, and commonly contain calcium.

Air-filled cysts must be differentiated from the cavitary lesions. Patients with a geographic history including the endemic area for coccidioidomycosis will pose the greatest problem as this fungus commonly gives rise to thin walled cavities and nearly two-thirds of those patients, so afflicted, give a history of hemoptysis. The cavitary lesions of the remaining fungal diseases as well as tuberculosis have, in most cases, a thicker wall and a surrounding infiltration. The wall of a cavitary carcinoma is thick and the cavity eccentric. Infarctions may cavitate; however, their sudden appearance and rapid change should lead to the proper diagnosis.

Pulmonary abscesses commonly have an air fluid level, but they generally change in appearance and a surrounding infiltration is the rule.

The expanding air filled bronchogenic cyst of the newborn and infant presents a special problem as it must be differentiated from congenital lobar emphysema, pneumatocele, tension pneumothorax, and diaphragmatic hernia. Congenital lobar emphysema occurs only in the upper or middle lobes, whereas bronchogenic cysts are much more frequently found in the lower lobes. In addition, lung markings are sometimes seen to pass through the former. A history of a recent pneumonia, particularly staphylococcal, is the rule when presented with a pneumatocele. These are found in the same lobe or lobes as the previous pneumonia and will usually regress spontaneously in a period of 3 to 4 weeks; however, some may remain for up to 9 months. This distinction is important because surgery is not indicated if a pneumatocele is present. One often is able to visualize the centrally placed collapsed lung when presented with a tension pneumothorax. Congenital diaphragmatic hernias are distinguished by the presence of multiple air filled loops of bowel within the chest in association with a notable decrease in the abdominal contents. On occasion, these loops are not apparent and intestinal contrast studies are necessary to make the correct diagnosis.

The differential diagnosis of a mediastinal bronchogenic cyst will depend chiefly upon its location. Only rarely does such a cyst arise from the trachea or main stem bronchi and extend into the anterior mediastinum; therefore, bronchogenic cysts need not be considered in the differential of anterior mediastinal masses.

In the superior mediastinum thyroid goiters, cystic hygromas, aneurysms, and lymphadenopathy, especially in a right paratracheal location, would be frequent considerations. Goiters often contain calcium and both they and cystic hygromas usually demonstrate a broad continuation with the soft tissue of the neck. Tracheal displacement by either is more common than by a bronchogenic cyst. Innominate artery buckling or aneurysms of the innominate artery, as well as aortic aneurysms, may show calcification within their walls and/or expansile pulsations on fluoroscopic examination. Isolated enlargement of a superior mediastinal lymph node is rare. Peritracheal lymphadenopathy, regardless of the etiology, is usually accompanied by a similar process in the peribronchial lymph nodes.

Neurogenic tumors are the prime consideration in paraspinal posterior mediastinal tumors. In contradistinction to these tumors, bronchogenic cysts do not cause rib spreading, bony erosion, or enlargement of the intervertebral foramina. Neuroblastomas frequently contain calcium and neuroenteric cysts are commonly associated with vertebral abnormalities, particularly hemivertebrae. Meningoceles also enlarge the intervertebral foramina and osteochondromas calcify. It is impossible to distinguish preoperatively between a duplication of the esophagus, leiomyoma, or other benign intramural, extramucosal tumors of the esophagus and a bronchogenic cyst in a similar location. The latter should be more strongly considered when presented with an extramural, extramucosal mass.

Of all the various locations where mediastinal bronchogenic cysts may be found, the subcarinal location is the most distinctive. Bronchogenic cysts account for by far the greatest majority of isolated masses in this area. Infrequently, these masses are found to be enlarged lymph nodes of infectious or lymphomatous origin. Angiography will be necessary to differentiate those cysts located in the remainder of the middle mediastinum from the various vascular abnormalities.

At times, a grossly calcified mediastinal mass is discovered in a subcarinal or less frequently a right paratracheal location. Usually such masses are proven to be either calcific lymph node complexes or are histologically so amorphous that a positive histologic diagnosis cannot be rendered. Infrequently, such a mass in the subcarinal region represents a teratoma.

Surgical extirpation upon discovery is the treatment of choice for any bronchogenic cyst regardless of its location.

SUMMARY AND CONCLUSION

The salient embryologic, pathologic, symptomatologic, and roentgenographic features of bronchogenic cysts have been reviewed. From an analysis of the roentgenograms of 46 cases, the following features are apparent: A bronchogenic cyst is a sharply defined, noncalcified, round or ovoid mass usually found within the lungs or mediastinum which does not appreciably change in size over a period of observation. In the lung fields, it may present as air filled cyst, cyst with an air fluid level, or as a homogeneous water density. The cysts characteristically have a thin wall. During the course of observation, a cyst may vary among any of the above three categories. Mediastinal bronchogenic cysts are almost invariably of a homogeneous water density. Although they are commonly attached to the trachea or main stem bronchi, they will rarely demonstrate an air fluid level. Their most distinctive location is in the subcarinal region.

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PULMONARY CONTUSION SECONDARY TO NONPENETRATING CHEST TRAUMA*

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PULMONARY contusion or bruise is an injury to the lung parenchyma without concomitant laceration. Although this entity has been known since the time of Morgagni,[10] an understanding of its mechanism of occurrence was not appreciated until recent times. Postmortem examination of war casualties, particularly blast injuries, and animal experimental efforts by many authors[3,4,5,8,11,12,14,26,27] revealed the potentiality of pulmonary contusion even in nonpenetrating chest injury. Earlier articles relating to contusion have described it as "contusion pneumonia" and "traumatic pneumonia." This terminology is thought to be inappropriate as it implies an infectious process.

Pulmonary parenchymal contusion is the most frequent roentgenographic finding in patients who have incurred major nonpenetrating thoracic trauma.[19,24] As indicated in Table I, although the association of fractures and pulmonary contusion is considerable, it is noted that contusion occurs more frequently than does a combination of fractures of the thoracic bony structures. In two sizable series, contusion was noted to occur 75.8 per cent and 72 per cent, respectively, in patients sustaining major nonpenetrating chest trauma.[19,24]

PATHOLOGIC FINDINGS

Pulmonary contusion may result from either direct or indirect trauma; direct trauma being that force primarily applied to the chest, whereas indirect trauma refers to transmitted forces as in blast injuries, deceleration, or the secondary force exerted by the abdominal contents against the diaphragm. Regardless of the specific type of trauma, the basic defect is a loss of vessel integrity.

Although direct chest trauma produces a greater incidence of pulmonary contusions, more fundamental information is available for the lung injury resulting from blast injury and in all probability the pathogenesis of both is similar. Hooker,[7] while studying the cause of the pulmonary bruising and rupture following animal exposure to TNT blast, speculated that the changes were a result of several factors. A lowering of alveolar pressure due to the suction wave would cause rupture of the alveolar capillaries. He stated that parenchymal injury also resulted from distention of the lungs with air during the positive phase of the blast and the direct impact of the pressure wave on the chest wall.

The work of Zuckerman[27] supported the

TABLE I

INCIDENCE OF PULMONARY CONTUSION COMPARED TO THAT OF FRACTURES OF THE BONY THORAX

Author	No. of Cases	Per Cent of Bony Thorax Fractures	Per Cent of Contusions
Westermark[19]	124	48.1	75.8
Williams	150	66.0	72.0

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latter hypothesis. This study showed that the compression wave was of shorter duration and of greater intensity than the suction wave, and in animals whose hemithorax was protected against such a compression wave no pulmonary changes were found, while the unprotected opposite hemithorax exhibited pulmonary hemorrhages.

Zuckerman also postulated that lung injury would result by transmission of a shock wave if the chest wall were flung inwards with a velocity of 66 feet per second acquired in 0.5 milliseconds or less. This supposition was confirmed by Stewart and associates[18] when animals were subjected to abrupt deceleration from terminal velocities up to 160 feet per second. In animals having a terminal velocity greater than 104 feet per second, diffuse pulmonary hemorrhage with subpleural emphysema, rib markings and occasional laceration resulted. With velocities from 75–104 feet per second, similar but more localized lesions were found. In those animals with velocities from 66–75 feet per second, the lungs were the site of multiple small scattered foci of hemorrhage.[18] If the velocity at impact is constant, large decelerative forces acting for a brief period produce injuries of greater severity than smaller forces acting over a longer period.

The nature of the blast components was substantiated by Carlton *et al.*[1] who demonstrated that the compression wave was of high positive pressure and shorter duration, while the suction wave was of less intense negative pressure acting over a longer period of time.

The phase of respiration has no decisive effect on the extent of resultant lung damage for the injury is due primarily to the direct shock wave impact.

The spectrum of pulmonary changes is similar irrespective of whether the force is rendered as a direct blow or indirectly as the result of a blast injury with the exception that blast injuries are usually bilateral.[14] Grossly, the lungs show hemorrhage with the amount, distribution, and character of this gross change correlating roughly with similar counterparts concerning the force. If the force is exerted over a small localized area, the hemorrhage is ordinarily focal, limited to the region of direct trauma, and produces a purple consolidation. If the force is expended over a longer area, the whole chest or hemithorax, the resultant contusion will be larger. Variations may exist. In some cases, especially younger people, rib markings in the form of subpleural hemorrhages result; in others there may be costophrenic angle contusion and in others massive hilar contusions.[8] Contre-coup injuries may result from anterior or lateral chest trauma with the contusion localized to the relatively fixed posterior portions of the lungs.[12] In addition to hemorrhage, the more severe pulmonary injuries may manifest as traumatic rupture of the alveoli[17] or as traumatic mediastinal emphysema.[26] In cases of less severe pulmonary injury, pulmonary edema with distention of the alveolar capillaries may result with only minimal hemorrhage, if any. While the majority of pulmonary contusions are the result of alveolar capillary damage with intra-alveolar extravasation, the rupture of larger vessels may fail to produce intra-alveolar hemorrhage but results in a dissection by the blood along the path of the vessel or bronchus. Three specific variations in the manifestation of pulmonary contusion exist. The most common is the intra-alveolar extravasation of blood producing a purple firm lesion which may be focal, segmental or lobar. More often it is focal and may be multiple. There may be special distributions as discussed (Fig. 1). Less intense injuries may produce focal areas of pulmonary edema, congestion of the capillaries, and a minimal variable loss of erythrocytes (Fig. 2). With loss of integrity of the larger pulmonary vessels, hemorrhage may not occur into the alveoli but may dissect along the soft tissues surrounding the vessels and bronchi (Fig. 3).

Variations in the extremes of pulmonary trauma with hemorrhage of the lung may

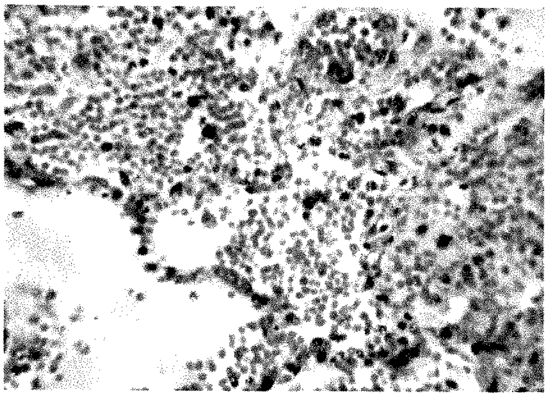

Fig. 1. A high power photomicrograph of a hematoxylin and eosin stained lung preparation showing extensive extravasation of erythrocytes into the alveoli, rupture of a small blood vessel into an alveolus, prominence of the alveolar walls and edema fluid. There is no evidence of inflammation.

not always be immediately apparent (see Fig. 4, *A* and *B*) on chest roentgenograms as shown in experimental animal studies,[15] and, when chest roentgenograms demonstrate hemothorax, the injury is most likely associated with some laceration and therefore more grave in its import.[9] Similarly, the lung which has pulmonary fat or tissue embolism is to be differentiated from primary pulmonary injuries and, in general, these have a poorer prognosis than pulmonary contusion with nonpenetrating trauma.[6]

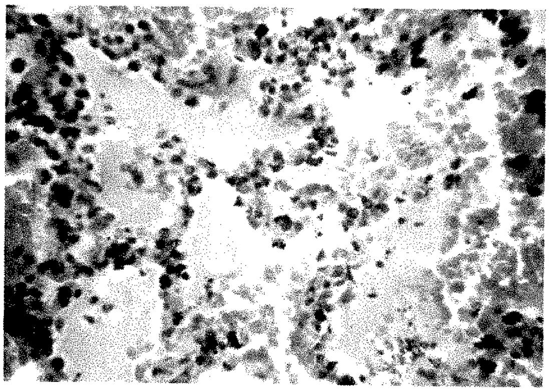

Fig. 2. A high magnification photomicrograph of a hematoxylin and eosin stained lung preparation demonstrating prominent alveolar walls housing distended capillaries. Within the alveolar lumens there is a protein-rich edema fluid with a small number of extravasated erythrocytes.

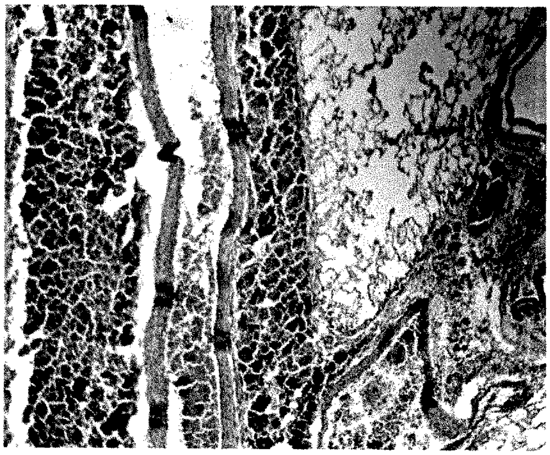

Fig. 3. A medium magnification photomicrograph of a hematoxylin and eosin stained lung preparation demonstrating perivascular soft tissue hemorrhage with adjacent uninvolved alveoli.

ROENTGENOGRAPHIC AND CORRELATIVE FINDINGS

Pulmonary contusion will usually be seen on the roentgenogram immediately following a nonpenetrating injury. Slight accentuation of the contusive changes may be found within the next few hours.

Figure 4*A*, the initial study immediately following a steering wheel injury, shows fractures of the right posterior second through seventh ribs and faint perihilar parenchymal densities representing early contusion. The chest roentgenogram 12 hours later (Fig. 4*B*) reveals increased opacification indicative of continued peribronchiolar and intra-alveolar hemorrhage.

Distribution on the roentgenogram may vary from diffuse bilateral changes to small localized areas. The diffuse changes are most commonly seen in crushing injuries or following exposure to blast. Pulmonary contusion does not usually conform to either the segments or lobes of the lungs; however, infrequently, it may be discrete and present in a segmental distribution. A triangular discrete area of contusion is noted in the anterior basilar segment of the right lower lobe in Figure 5, *A* and *B*, following a fall and blow to the right anterior chest.

Depending on the basic pathologic type

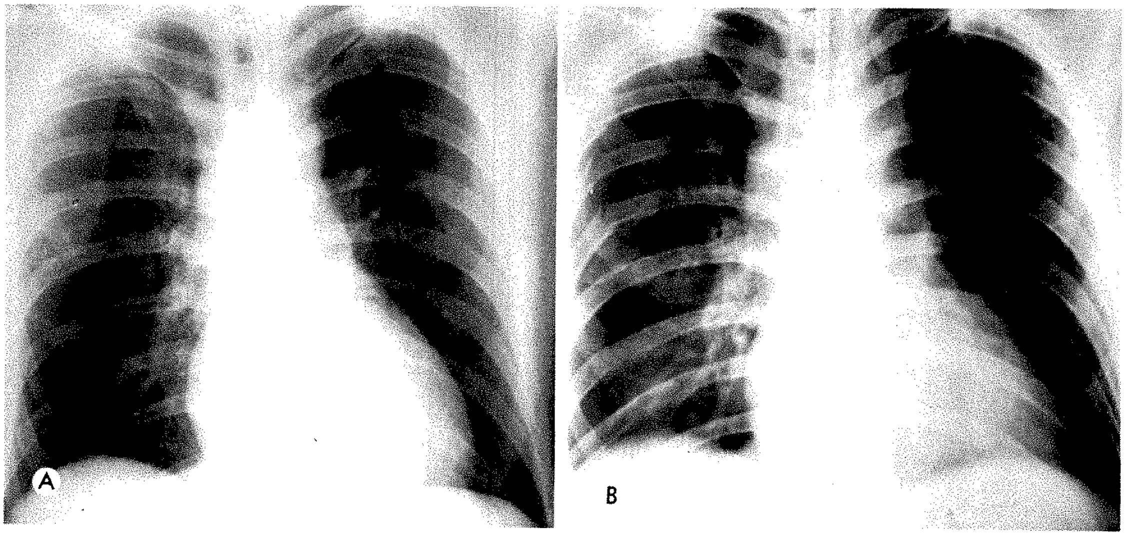

Fig. 4. (*A*) Roentgenogram of the chest immediately following an automobile accident shows fractures of the right posterior second through seventh ribs. Very early changes of contusion are noted within the right perihilar area. (*B*) Roentgenographic study 12 hours following *A* shows the contusive changes to be accentuated, indicating continued peribronchiolar and intra-alveolar hemorrhage.

of pulmonary contusion, the roentgenogram may show either an irregular nodularity or the contusion may present as a homogeneous consolidation. Frequently, both appear simultaneously.

Peribronchiolar or perivascular hemorrhage results in either isolated or confluent irregular nodular densities.

Figure 6 is the chest roentgenogram of a patient who was run over by a tractor. No fractures were present but diffuse small irregular opacities are apparent within the lungs and represent perivascular and peribronchiolar hemorrhage. The roentgenographic appearance of this type of contusion is indistinguishable from that of a peribronchiolar pneumonic infiltrate.

Intra-alveolar hemorrhage or edema pro-

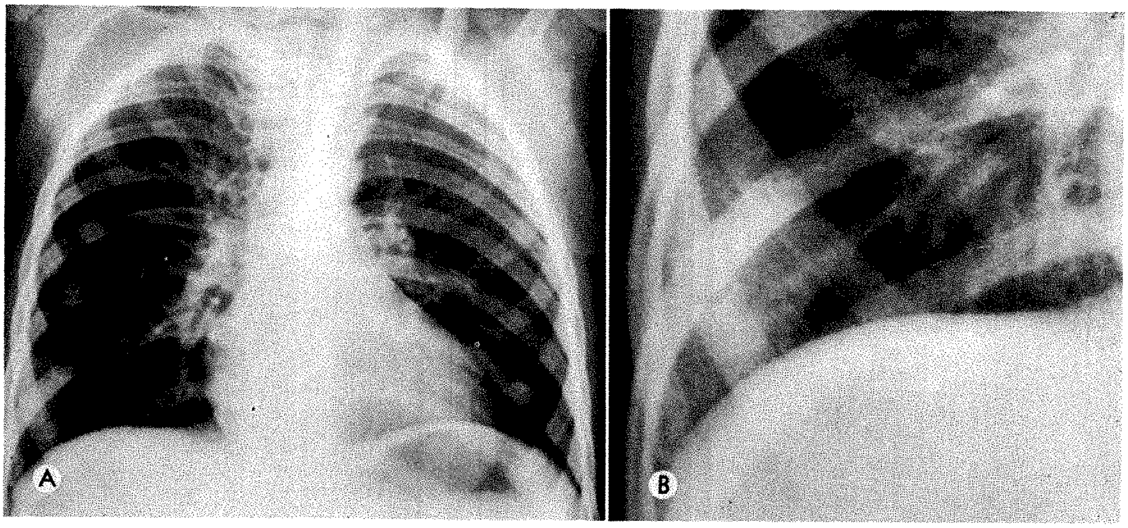

Fig. 5. (*A*) Chest roentgenogram following injury to the right lower thorax shows a well demarcated homogeneous area of contusion in the area of the anterior basilar segment of right lower lobe. (*B*) Close-up of *A*.

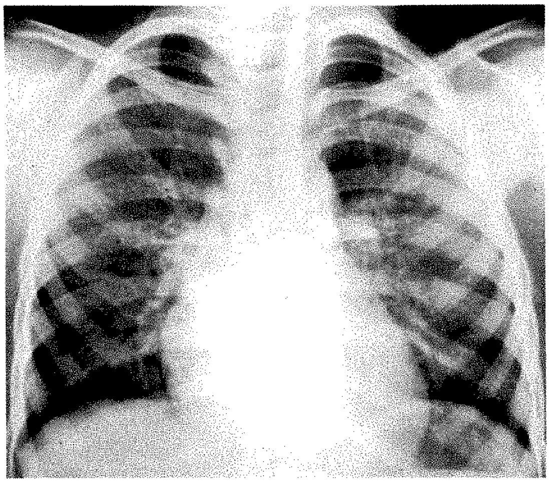

Fig. 6. Chest roentgenogram taken after patient was run over by a tractor shows diffuse irregular punctate opacities representing perivascular or peribronchiolar hemorrhage.

duces a homogeneous opacification on the roentgenogram. Differentiation may be made only by the rapidity of roentgenographic resolution. The opacification from edema may have very rapid resolution. Figure 7*A*, the initial chest roentgenogram, shows an extensive homogeneous opacification within the right lung following a sudden compression of the right chest dealt by a falling horse. The contusion almost completely resolved 24 hours following injury (Fig. 7*B*). The peribronchiolar, perivascular, or intra-alveolar hemorrhage may take longer in its resolution. Even though extensive, however, it may show surprisingly rapid clearing on the roentgenogram, as it has been noted that pulmonary contusion will almost invariably clear within a 10 day period.

The time of resolution is most important when contusion is present and superimposed pneumonia is suspected. The roentgenographic differentiation of these two entities is impossible. However, with knowledge of the resolution time for contusion, one should suspect a superimposed pneumonia if the roentgenogram does not clear in the appropriate time. Obviously, if the roentgenographic changes are accentuated subsequent to the initial studies, superimposed pneumonia is present.

Another post-traumatic complication to be differentiated from pulmonary contusion, particularly the perivascular and

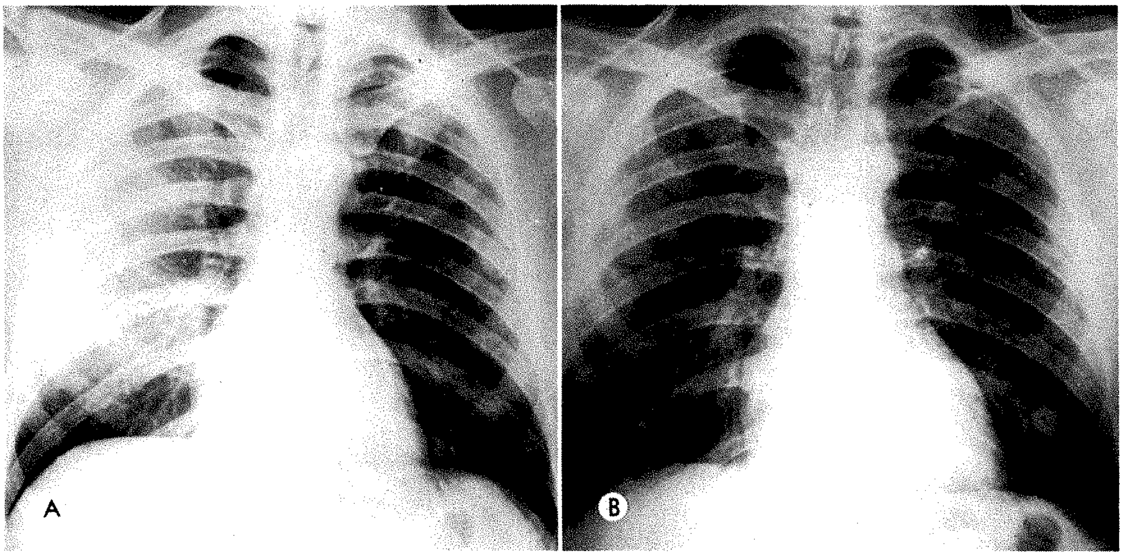

Fig. 7. (*A*) Chest roentgenogram following a crushing injury shows diffuse homogeneous opacification within the right lung, indicating either intra-alveolar hemorrhage or exudation. (*B*) Follow-up study 24 hours after *A* shows almost complete resolution of the pulmonary opacification, indicating that the majority of the contusion was exudation. Minimal residual contusion is apparent in the lateral segment of the right middle lobe and anterior segment of the right upper lobe.

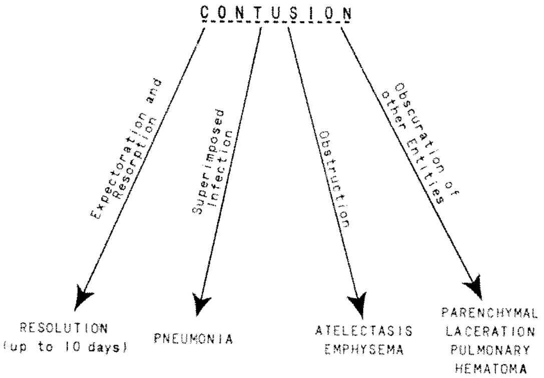
CONTUSION
Expectoration and Resorption
Superimposed Infection
Obstruction
Obscuration of other Entities
RESOLUTION (up to 10 days)
PNEUMONIA
ATELECTASIS EMPHYSEMA
PARENCHYMAL LACERATION PULMONARY HEMATOMA

Fig. 8. A schematic drawing showing the importance of recognizing pulmonary contusion on the roentgenogram and also the subsequent findings which may be apparent as a result of contusion or may be obscured.

peribronchiolar type, is that of fat embolization. This entity is manifested on the chest roentgenogram usually between the first and third days following injury. The roentgenographic appearance is that of a diffuse bilateral haziness similar to pulmonary edema. The pulmonary vasculature may reveal prominence with faint punctate densities appearing contiguous with the vascular markings. Roentgenographic clearing of fat embolization is a slower process than that of contusion with the majority of cases showing resolution after a 1 to 4 week period.

Contusion may mask a considerable number of entities which result from nonpenetrating injury.[23] Figure 8 shows a chronologic sequence of events resulting from contusion. Resolution may occur within the described period of time. Pneumonia may subsequently be superimposed. As resolution occurs, one may become aware of other entities within the lung such as parenchymal laceration and pulmonary hematoma, both a result of nonpenetrating injury. Contusion may cause other findings within the lung such as emphysema and atelectasis. These entities result from obstructive changes caused by either intrabronchial or peribronchial hemorrhage of contusion. Resolution of emphysema and atelectasis is commensurate with relief of the obstructing clot.

SUMMARY

The various types of pulmonary parenchymal contusion, such as perivascular, peribronchial and intra-alveolar hemorrhage or exudation, have been reviewed and correlated with the roentgenologic appearance of each. The time of appearance and resolution of contusion following injury is discussed. Other entities peculiar to nonpenetrating chest trauma which may be obscured by contusion are briefly mentioned.

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THE VALUE OF PNEUMOPERITONEUM IN DIAGNOSIS OF SEQUESTERED LUNG

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SEQUESTRATION of the lung is a rare but important entity. In cases of this condition, where the correct diagnosis has not been made preoperatively, serious, even fatal, bleeding has occurred at surgery. In a recent case this diagnosis was considered because of the appearance of the plain chest roentgenograms. Pneumoperitoneal study was made preoperatively and demonstrated the anomalous systemic vessel characteristic of sequestered lung. The value of this procedure in establishing this diagnosis has not, to our knowledge, been previously reported.

Sequestration of the lung is a congenital anomaly of the lower lobe in which lung tissue has abnormal bronchial and arterial connections. The sequestered portion of the lung is supplied by a systemic artery. This artery arises from the aorta and usually anastomoses with normal pulmonary arteries. In most reported cases no patent connection between the sequestered lung and the bronchial tree has been demonstrated either by bronchography or in the gross surgical specimen. In some of these cases, however, the sequestered lung has contained air indicating a microscopic bronchial connection. The sequestered lung may be composed of normally differentiated lung tissue, a polycystic mass, one or more bronchogenic cysts or a mass containing branching bronchi. It may be within the visceral pleura of the involved lower lobe (intralobar) or it may lie adjacent to the lower lobe enclosed in a separate pleural sheath (extralobar). In intralobar sequestration the venous drainage is to the pulmonary veins, whereas in extralobar sequestration it is to the systemic veins. Extralobar sequestration will not be discussed further.

Intralobar sequestration commonly presents clinically in one of two ways. It is either detected as an incidental finding on a chest roentgenogram or presents as a picture of recurrent infection in the same place in one of the lower lobes. Wyman and Eyler,[20] in their discussion of 7 cases of intralobar sequestration, state that 3 were asymptomatic and 4 symptomatic. The 3 asymptomatic patients all had homogenous masses. In 2 of these 3 a finger-like projection pointing toward the aorta was seen on the plain chest roentgenograms. They postulate that this projection represented the systemic artery supplying the sequestered lung. They believe that when such a projection is seen it should suggest the diagnosis. All 4 symptomatic patients, at times, showed thin walled cysts which contained both fluid and air.

Other authors refer to the preoperative diagnosis by aortography or refer to the inadvertent preoperative diagnosis by injection of contrast medium into the sequestered portion of the lung. Instead of outlining the suspected abscess cavity, a mass of branching bronchi was outlined. In some reported cases the correct diagnosis was not made until the systemic artery had been inadvertently cut at surgery (with serious resultant hemorrhage).

Beneke[1] put forward the view that pulmonary sequestration is a primary developmental anomaly and that the anomalous blood supply is secondary. Pryce,[15] on the other hand, holds the opposite view that the anomalous vessel is the primary abnormality. This vessel could then "cap-

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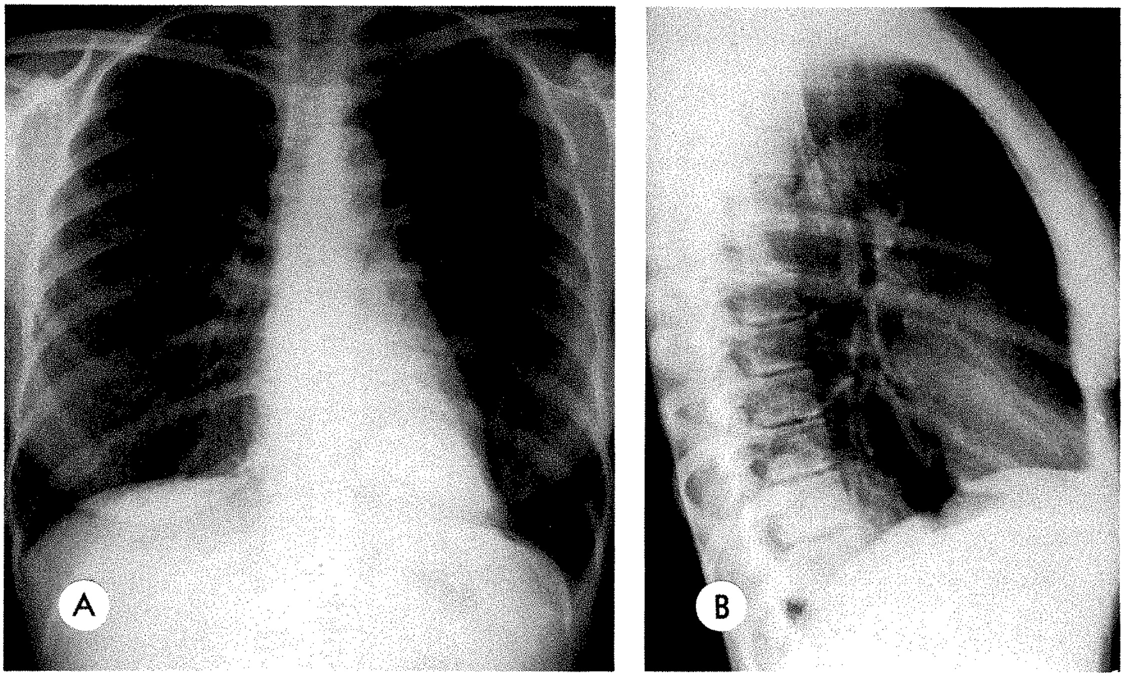

FIG. 1. (*A*) Posteroanterior and (*B*) lateral chest roentgenograms show the paravertebral mass immediately adjacent to the left hemidiaphragm. This appearance is identical to that shown on roentgenograms made elsewhere 5 months earlier. There are no erosive changes in the ribs or vertebrae. There is no evidence of an anomalous vessel.

ture" an end bud of normally developing pulmonary tissue. We believe the pathologic findings in the case presented here support the latter view that the anomalous artery is the primary abnormality.

REPORT OF A CASE

L.G., a 39 year old white female, was admitted to San Francisco General Hospital in January, 1963 for investigation of a left chest mass. This had been detected 5 months earlier at another hospital on a routine chest roent-

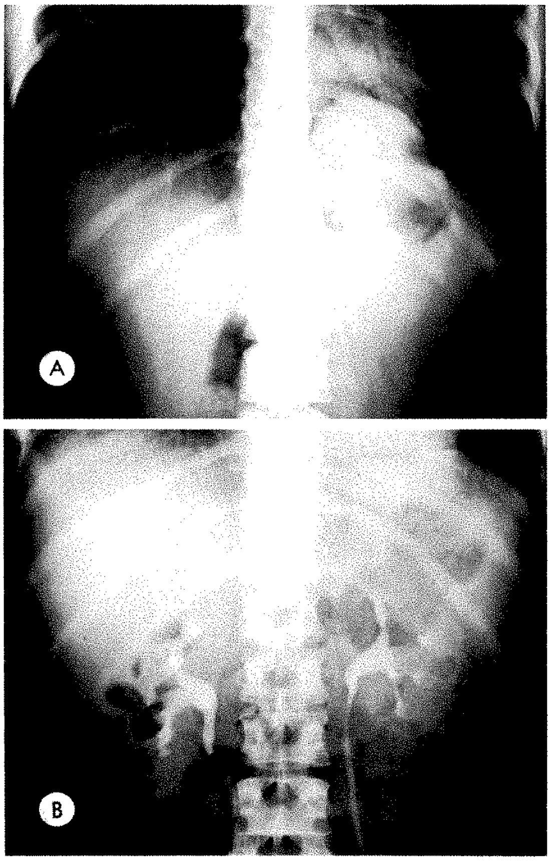

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FIG. 2. (*A*) Plain roentgenogram and (*B*) 10 minute intravenous pyelogram. They show that the mass is not a thoracic kidney. The plain roentgenogram also shows streaky densities in the lung above the mass. This portion of the lung showed pneumonitis and bronchiectasis in the pathologic specimen.

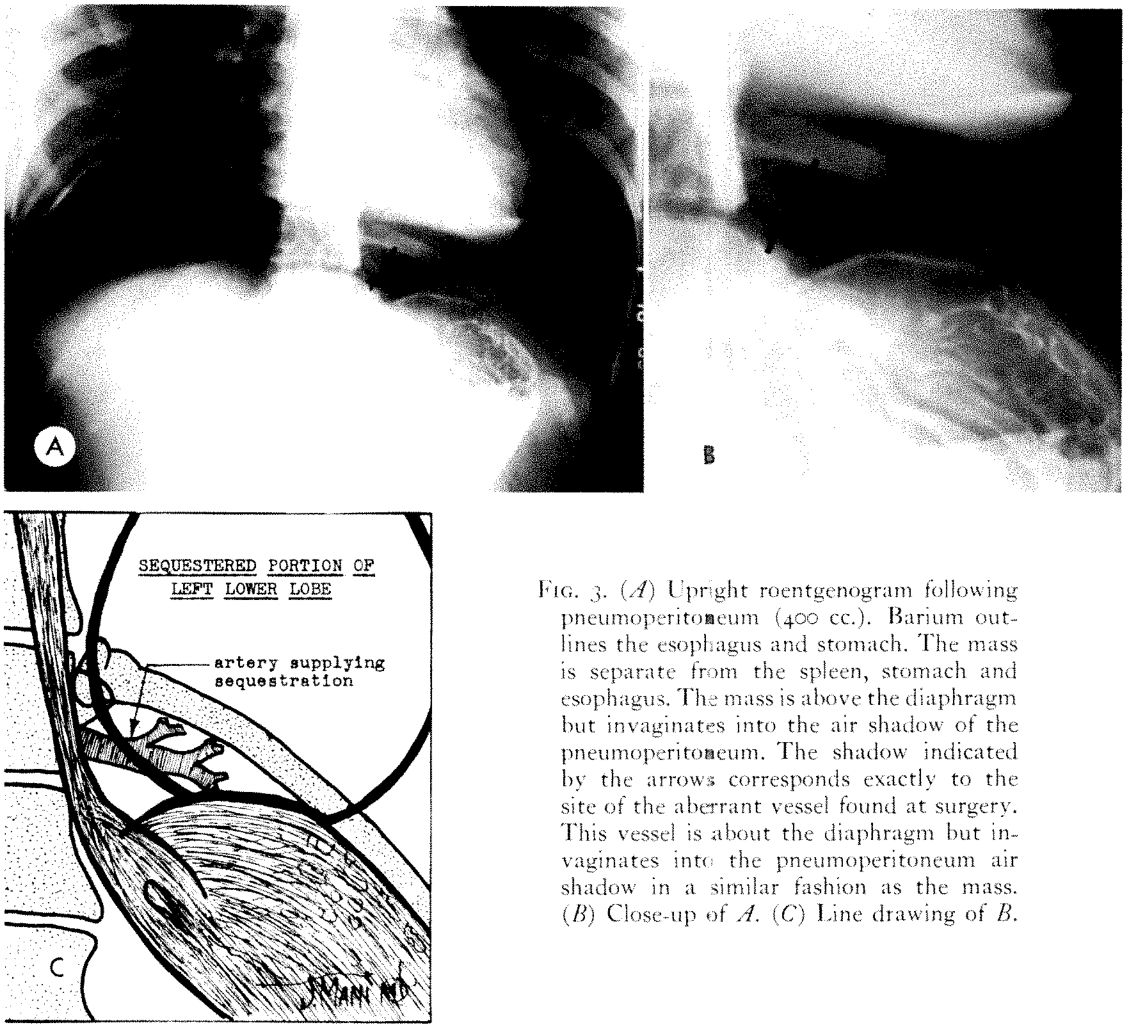
A
B
SEQUESTERED PORTION OF LEFT LOWER LOBE
artery supplying sequestration
C

Fig. 3. (*A*) Upright roentgenogram following pneumoperitoneum (400 cc.). Barium outlines the esophagus and stomach. The mass is separate from the spleen, stomach and esophagus. The mass is above the diaphragm but invaginates into the air shadow of the pneumoperitoneum. The shadow indicated by the arrows corresponds exactly to the site of the aberrant vessel found at surgery. This vessel is about the diaphragm but invaginates into the pneumoperitoneum air shadow in a similar fashion as the mass. (*B*) Close-up of *A*. (*C*) Line drawing of *B*.

genogram during pregnancy. The patient had no chest symptoms at this time and when informed of the discovery of the mass decided, at first, to have nothing done. Later she began to worry about the possibility of having cancer and presented herself for investigation.

On admission to this hospital she had no other complaints. Her only previous operations were tonsillectomy and left mastoidectomy, both in childhood. The family history was noncontributory.

On examination she appeared well. Vital signs were normal and her blood pressure was 109/72. There was no cyanosis or clubbing. No unusual skin pigmentation was noted. Examination of the chest showed dullness and diminished breath sounds over the left base posteriorly but there were no adventitious sounds. All other systems showed no important findings. Urinalysis and blood count were within normal limits. The preoperative roentgenographic findings are shown in Figures 1 through 3, inclusive. Figure 4 is a pneumoperitoneum study made after surgery.

Surgical Procedure and Findings. A left thoracotomy through the 6th interspace revealed a mass occupying the posterior basal segment of the lower lobe. The mass was 9 cm. in greatest diameter and appeared to compress adjacent lung tissue. There were a few filmy pleural adhesions over the mass and over the rest of the lower lobe. A large pulsating artery 1 cm. in diameter and 4 cm. in length entered the posterior and inferior portion of the mass. The artery arose from the aorta immediately above the diaphragm and was enclosed in a posterior extension of the inferior pulmonary ligament. There was no accompanying vein

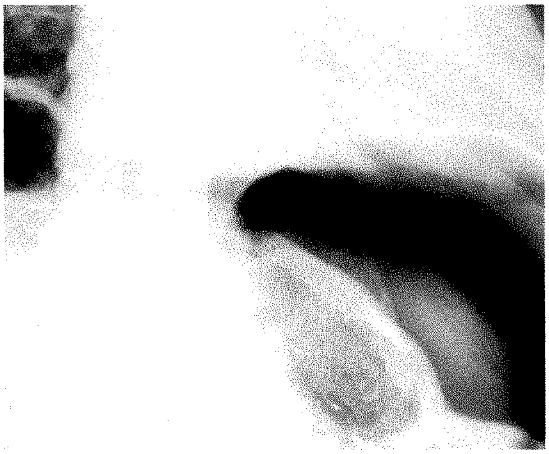

Fig. 4. Pneumoperitoneum study 2 months after surgery. The anomalous vessel is no longer seen.

of comparable size. No other abnormalities were noted. After ligation and division of the anomalous artery, a left lower lobectomy was performed (Fig. 5, *A* and *B*).

Pathologic Specimen. The roentgenograms of the specimen injected with opaque media are shown in Figure 6, *A* and *B*. When the specimen was cut, the mass in the posterior basal segment was found to be a cyst filled with sterile yellow fluid. The cyst was lined by a corrugated membrane and at the apex of the cyst was an area of dense white scar tissue (Fig. 5*B*). A probe was passed from the apex of the cyst through a small bronchus which coursed through the scarred area. This bronchus was a division of the posterior basal bronchus. A branch of the systemic artery was found to encircle this small bronchus for almost 360° and appeared to compress it and occlude it. This encircling artery is shown on the injection specimen (Fig. 6*A*).

Microscopic examination of sections through the cyst showed a lining of bronchial epithelium. The surrounding lung parenchyma was collapsed and completely obliterated by necrotic cellular debris. It contained dilated bronchi and bronchioles and was infiltrated with

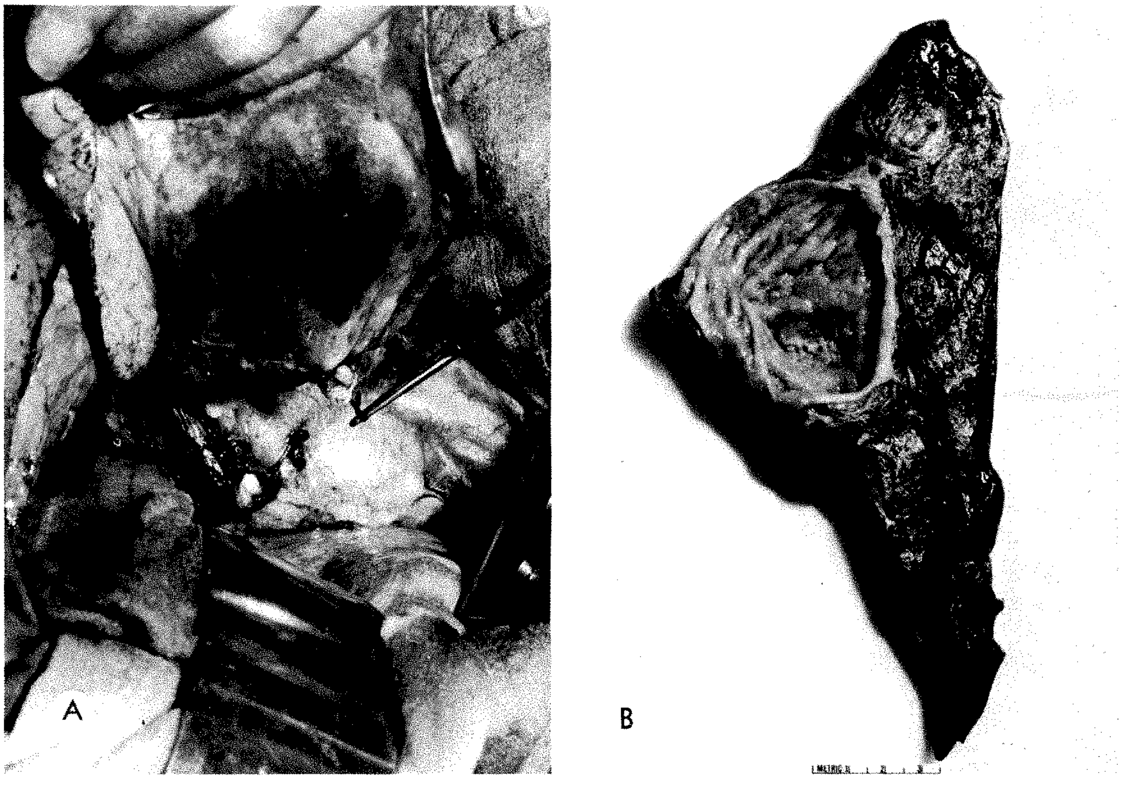

Fig. 5. (*A*) A photograph taken at surgery. The cut ends of the anomalous vessel are shown tied by ligatures. The retractor is on the diaphragm and the left lower lobe is being held forward. (*B*) The resected left lower lobe after the cyst had been opened. The diaphragmatic surface of the lobe is below, the posterior surface above and the anterior surface on the right. Note the corrugated lining of the cyst and the scarred area above the cyst.

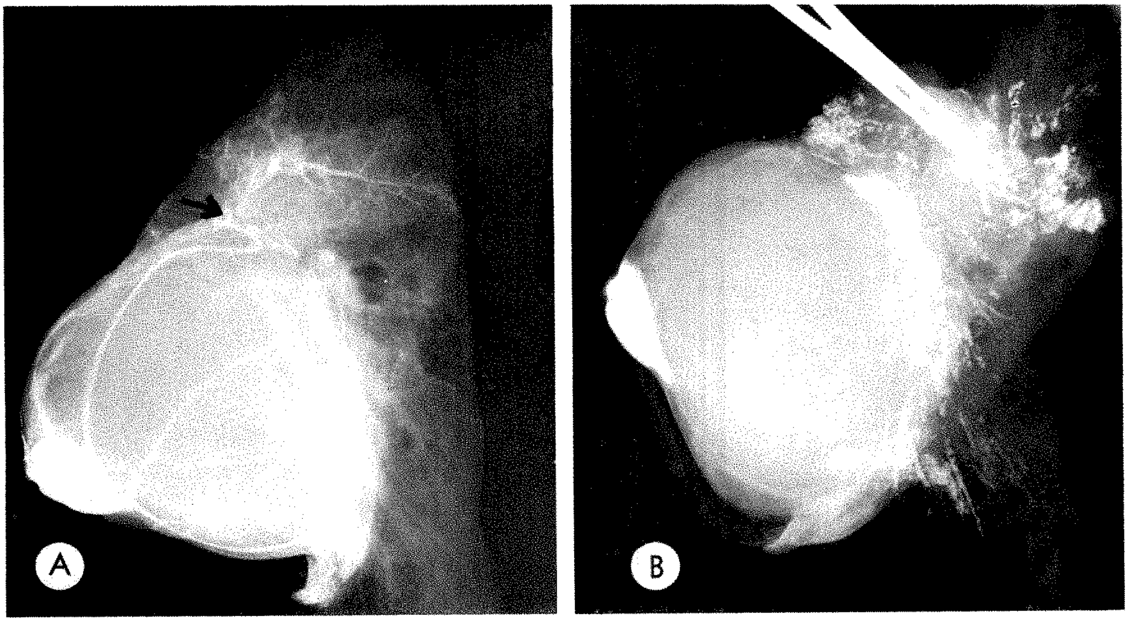

FIG. 6. (*A*) Roentgenogram of the surgical specimen. The systemic artery has been injected with hypaque. Branches of the systemic artery run over the cystic mass. The arrow points to where one branch of the systemic artery completes almost a 360° turn around the bronchus going to the sequestered lung. Note that a branch of the pulmonary artery has filled with contrast medium indicating that the systemic artery anastomoses with it. The pulmonary veins are also opacified (compare with *B*). (*B*) Roentgenogram of the specimen with the bronchial tree injected with pantopaque. There is no pantopaque entering the cyst. (Some contrast medium remains in the systemic artery from the previous arterial injection.)

chronic inflammatory cells. The encircling branch of the systemic artery showed the typical muscular architecture of a small artery, whereas the systemic artery itself had numerous elastic lamina, thus simulating the appearance of the aorta or pulmonary artery.

Pathologic Diagnosis. Intralobar sequestration of the lung, with bronchiectasis and chronic pneumonitis of the left lower lobe.

DISCUSSION

In this case of intralobar sequestration, it would appear that the anomalous vessel has been demonstrated by pneumoperitoneum roentgenography for the first time. This is a simple procedure. If properly performed it has virtually no risk. Moretz and Erickson[14] mention a report of over 300,000 pneumoperitoneum studies without incidence of hemorrhage or peritonitis. The value of pneumoperitoneum in establishing the diagnosis of masses adjacent to the diaphragm has been known for many years. In such cases it may be impossible to decide from the plain chest roentgenograms whether the mass is entirely within the chest, or is a herniation of abdominal contents. In this situation a pneumoperitoneum study should be made and upright roentgenograms obtained. The authors wish to draw attention to the possibility of an anomalous vessel being visible in the pneumoperitoneum air shadow and suggest that radiologists specifically look for it. If this vessel is seen, it will establish the diagnosis of sequestered lung. In previously reported cases of intralobar sequestration coming to surgery, the anomalous artery has almost invariably been in the paravertebral gutter close to the diaphragm and more commonly on the left side. Other shadows should not cause confusion with that of an anomalous vessel. The crus of the diaphragm runs in a characteristic location and adhesions are usually fan-shaped or irregular. They do not resemble the tubular shadow of a vessel. The roentgenograms were reviewed of 20 patients who had had a pneumoperitoneum, either performed therapeutically for upper lobe tuberculosis, or resulting from a perforated peptic ulcer. In none of these 20 cases was there a shadow similar to that caused by the abnormal vessel in this patient.

The pathologic specimen in this case gives an unusually clear demonstration of the encirclement and occlusion of the bronchus to the sequestered lung by a branch of the systemic artery. It would appear unlikely that the artery happened to grow around the bronchus at the site where it was previously constricted. A much more likely proposition would be that the artery interfered with the bronchial connections of the sequestered lung. This is strong evidence for the viewpoint that the anomalous artery is the primary abnormality.

SUMMARY

1. The importance of preoperative diagnosis in cases of intralobar sequestration is stressed.

2. The major findings on previously reported cases of this condition are noted.

3. A new finding on pneumoperitoneum studies is reported.

4. The structure of the pathologic specimen is analyzed and throws light on the primary abnormality in this condition.

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THE VALSALVA MANEUVER IN ROENTGENOLOGIC DIAGNOSIS

By JOSEPH E. WHITLEY, M.D.,* *and* JAMES F. MARTIN, M.D.
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WHETHER airway straining when used as a clinical method to evaluate a subject's cardiovascular responses should be termed the Valsalva maneuver or, as suggested by Derbes and Kerr,[4] Weber's experiment is problematic. In 1704, Valsalva[18] described a procedure of blowing against the closed mouth and nose as a diagnostic and therapeutic means in patients with middle ear disease and tympanic membrane perforation, while Weber[19] in 1851 was the first to describe the alterations in heart sounds and pulse associated with blowing against a closed glottis. In this report, the more common usage is employed.

The mechanism of the Valsalva maneuver and the resultant physiologic responses have been fairly well established.[3,7,11] The response to airway straining is an increase in intrathoracic pressure with a resultant lowering of the effective filling pressures of both ventricles. The relative importance of the factors resulting in the lowering of effective filling pressures, particularly in cardiovascular disease states, is open to some debate; however, in normal subjects it is generally agreed that the effect is principally due to obstruction of venous return to the right heart associated with slowing of the flow of blood in the central venous reservoir[15] (right atrium, venae cavae and hepatic veins), and reversing venous flow in some limited venous beds.[2] There is a subsequent diminution in the effective mean and pulse pressures in the pulmonary artery and in the effective pressure in the pulmonary capillary bed. There is an initial transient elevation in stroke volume as blood is expelled from the left heart and the pulmonary veins by the increased intrathoracic pressure. Then, with the decrease in venous return from the lungs and concurrent diminution in effective filling pressure of the left heart, there is a resultant reduction in cardiac output of about 30 to 50 per cent with the technique as employed in most laboratories. This phenomenon is evidenced by an initial brief rise followed by a sustained decrease in mean and pulse pressure in the aorta. These alterations trigger a reflex increase in sympathetic tone with peripheral vasoconstriction and an increase in heart rate. After 8 to 10 seconds, a secondary recovery toward control pressure and output is usually noted.

With a sudden release of airway straining, there is a temporary "overshoot" in mean and pulse pressures and in the flow into the right heart. Two to three cardiac cycles later, this "overshoot" is transmitted to the left heart. This temporal phenomenon has been used to differentiate left and right heart murmurs by the sequence with which the murmurs reach maximum intensity after a sudden release of airway straining.

Other clinical uses of the cardiovascular responses to the Valsalva maneuver and the period immediately following release are numerous. It has been employed as a test of adequacy of a patient's sympathetic responses,[17,21] and as a test to diagnose left heart failure and other causes of pulmonary venous hypertension.[6,16] The effect of the Valsalva maneuver on splitting of the second heart sound and its effect on arterial saturation have been described as useful in differentiating the normal heart from certain congenital cardiac abnormalities.[1,8,11]

In the field of radiology, the Valsalva maneuver (and increasing intrabronchial pressure via an endotrachial tube) has been employed in conjunction with angiocardiography and arteriography to temporarily lower the cardiac output, thus improving the visualization of the pulmonary vascular bed, the aorta and its principal branches including the coronary arteries.[13,14] The use of the post-pressor phase of Valsalva maneuver has been described as a method to temporarily reverse left to right shunts at the atrial level, and thus allow demonstration of atrial septal defects angiocardiographically with right atrial injection.[9]

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* Senior Investigator in Clinical Research, North Carolina Heart Association.

The use of the Valsalva maneuver for plain roentgenography in diagnostic radiology dates back to at least 1928.[12] Its leading recent proponent is Westermark[20] who proposed its adoption as a part of the routine examination of the chest. He felt that it was valuable in the study of pulmonary lesions and to confirm or refute the presence of pulmonary arterial hypertension. Obtaining conventional posteroanterior roentgenograms of the chest during the "overshoot" period, following the release of the Valsalva maneuver, has more recently been proposed as a method for improving the visualization of an enlarged left atrial appendage in mitral stenosis.[10] Having come full circle to Valsalva's original concept of the procedure, the maneuver was lately described as a method by which to fill the eustachian tubes with contrast material.[22]

The procedure has been used in conjunction with chest roentgenography in our department for 4 years and in more than 2,000 selected cases.

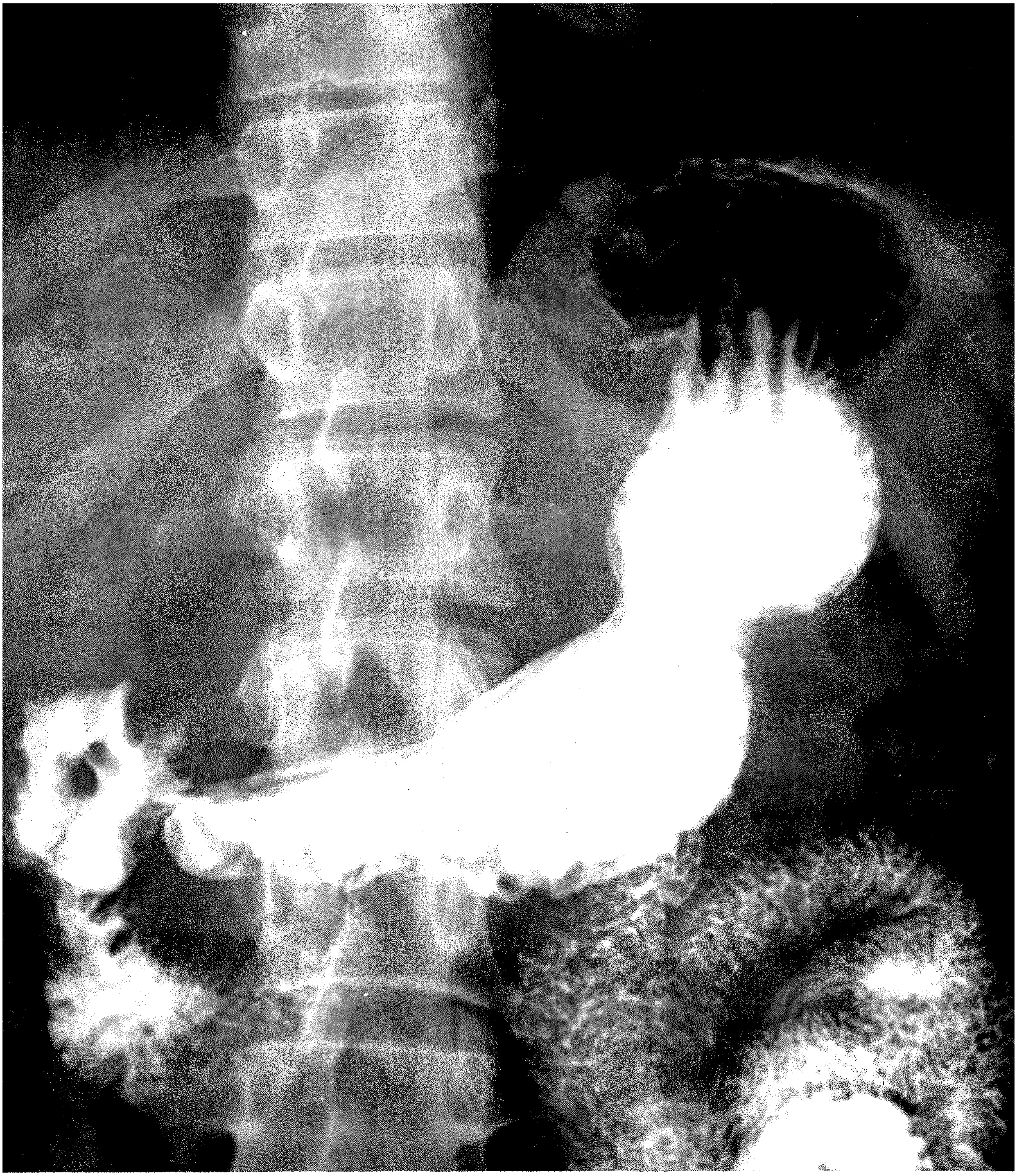
METHOD

The technique employed at this institution consists of the patient taking a deep breath, forcibly blowing into a mercury manometer and maintaining the expiratory effort. The mercury column of the manometer is positioned to superimpose over the edge of the posteroanterior chest film and thus record the instantaneous pressure at the moment when the roentgenogram is obtained. The exposure is made approximately 5 to 6 seconds after the initiation of the patient's effort.

The minimum level of intrabronchial pressure to assure a consistent significant cardiovascular response in the normal person has been variously estimated to be in the range of 30 to 40 mm. of mercury. The precise level in any individual is determined by his pulmonary compliance, venous pressure, and vasomotor tone.[16]

From the collected published cardiac catheterization data, it was noted that the time of maximum physiologic response to the Valsalva maneuver occurs in the range of 6 to 8 seconds after the intrabronchial pressure is elevated. To estimate how this reported time of maximum physiologic response coincides with the timing of the maximum anatomic response as found with the roentgenographic technique, a cineradiographic examination of the heart was undertaken with filming during normal respiration, during the Valsalva maneuver as long as it could be sustained without syncope, and during the succeeding 10 to 12 seconds after release. Ten subjects without known cardiac disease were studied with this procedure in the erect position, employing the posteroanterior projection. Simultaneously, an electrocardiogram was obtained and the "pressure blown" was recorded with a Statham strain gauge on a multichannel chart recorder with a known time scale. The data obtained are shown in Figure 1. The mean interval from the onset of the Valsalva maneuver to minimum heart size as seen on the posteroanterior roentgenogram was 4.9 seconds.

In order to more easily ascertain the minimum level of positive pressure sustained and to make the timing of the procedure more convenient, a simple device was manufactured (Fig. 2) and connected in parallel with the mercury manometer. When a pressure of 30 mm. Hg or more is reached, the device was designed to turn on a light visible to the subject and activate a timing circuit. When the pressure has been sustained for 5 seconds, the timing



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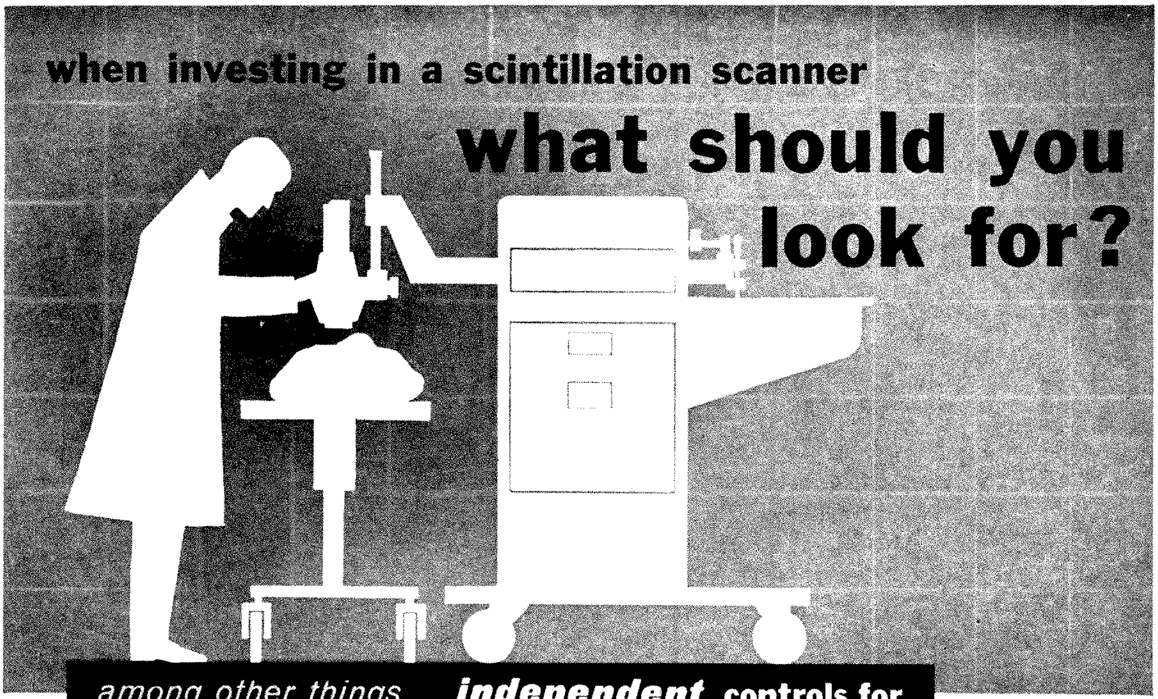
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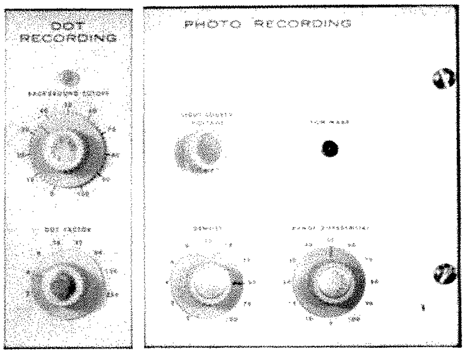

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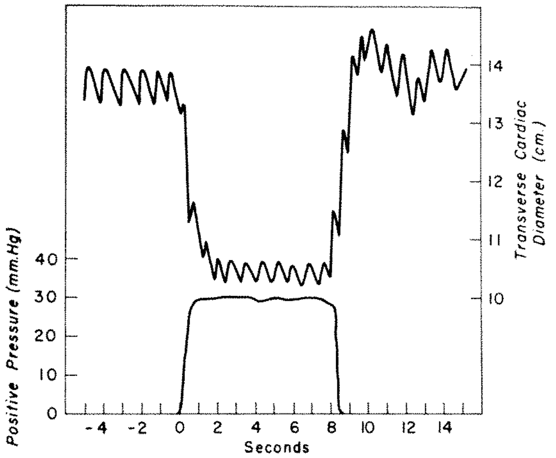

Fig. 1. The response of the heart of a normal individual to the Valsalva maneuver. The upper tracing of the transverse diameter was obtained from projecting a simultaneous cine examination of the heart and replotting over the lower tracings obtained with a Stathum strain gauge.

mechanism turns on a second signal light which is visible from the control booth. If the pressure falls below the 30 mm. Hg, the timing mechanism is automatically recycled. Most of the accompanying roentgenograms were obtained prior to the installation of this refinement.

RESULTS

In normal individuals (patients without known cardiovascular or pulmonary disease and personnel routinely examined), the heart and great vessels significantly diminish in size with an associated diminution in the pulmonary vasculature and increased radiolucency in the lungs during the positive pressure phase of the Valsalva maneuver. After release of the positive pressure, there is a transient increase in the size of these structures above pre-maneuver measurements presumably associated with the temporary elevation in cardiac output. Since the routine roentgenograms were not timed in reference to the heart cycle, no statistical analysis of these variations was attempted. Diminution in the transverse diameter of the heart in the order of 15 to 30 per cent was routinely encountered with diminution of similar magnitude noted in the great vessels (Fig. 3, *A* and *B*; and 4, *A* and *B*).

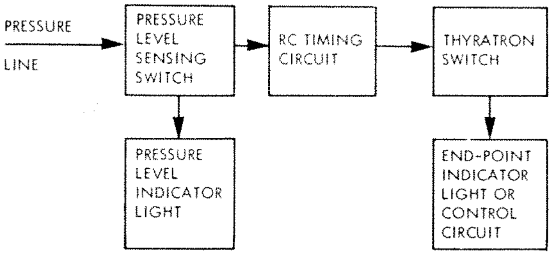
PRESSURE
LINE
PRESSURE LEVEL SENSING SWITCH
RC TIMING CIRCUIT
THYRATRON SWITCH
PRESSURE LEVEL INDICATOR LIGHT
END-POINT INDICATOR LIGHT OR CONTROL CIRCUIT

Fig. 2. Schema of the pressure-time indicator device designed by Dr. F. L. Thurstone, Department of Biomedical Engineering, Bowman Gray School of Medicine.

The clinical conditions in which roentgenograms made during the positive pressure phase of the Valsalva maneuver have been found useful are:

1. In differentiating large hilar vessels from hilar lymphadenopathy and other mass lesions of the hilus by improving the visualization of apparent hilar masses (both posteroanterior and lateral projections have proved helpful) (Fig. 5, *A* and *B*; and 6, *A* and *B*).

2. In improving the visualization of miliary and small nodular pulmonary densities and to help differentiate normal and dilated blood vessels from infiltration and fibrosis (Fig. 7, *A* and *B*).

3. In providing an additional approach to the diagnosis and evaluation of certain abnormal cardiovascular conditions. In cases of simple mitral valvular lesions, of uncomplicated small and moderate sized left to right shunts, and of emphysema and fibrosis without accompanying pulmonary hypertension, a response similar to that described in normals is encountered. With positive pressure there is an apparent regression of the characteristic roentgenographic findings in these various states, making the appearance of the heart and great vessels more normal (Fig. 8, *A* and *B*; and 10, *A* and *B*). In left to right shunts and mitral valvular disease complicated with pulmonary hypertension, as well as

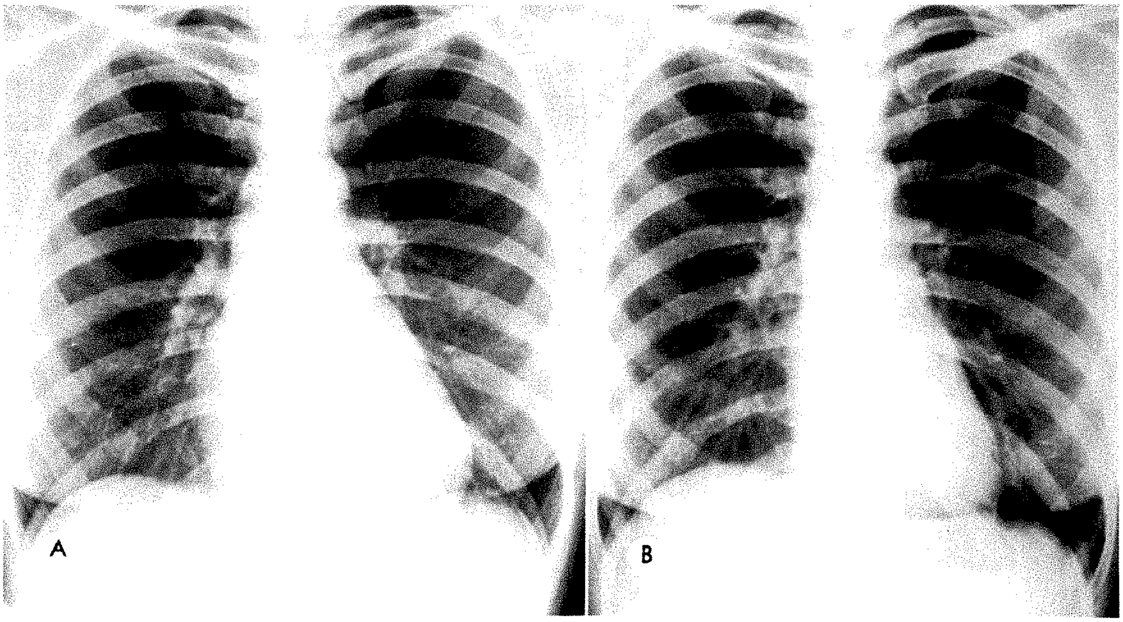

Fig. 3. (*A* and *B*) Normal Valsalva response accentuated by mild iron deficiency anemia (Hb. 9.9 gm., Hct. 35 per cent) in a 31 year old female.

primary pulmonary hypertension and cor pulmonale, the abnormalities of the pulmonary vascular tree appear fixed despite positive pressure and some diminution in heart and aortic size (Fig. 9, *A* and *B*; and 11, *A* and *B*). However, a lack of change in the appearance of the pulmonary vasculature with positive pressure is not pathognomonic of pulmonary hypertension. Such a lack of change has been observed in valvular pulmonary stenosis, intra-atrial septal defects with massive left to right

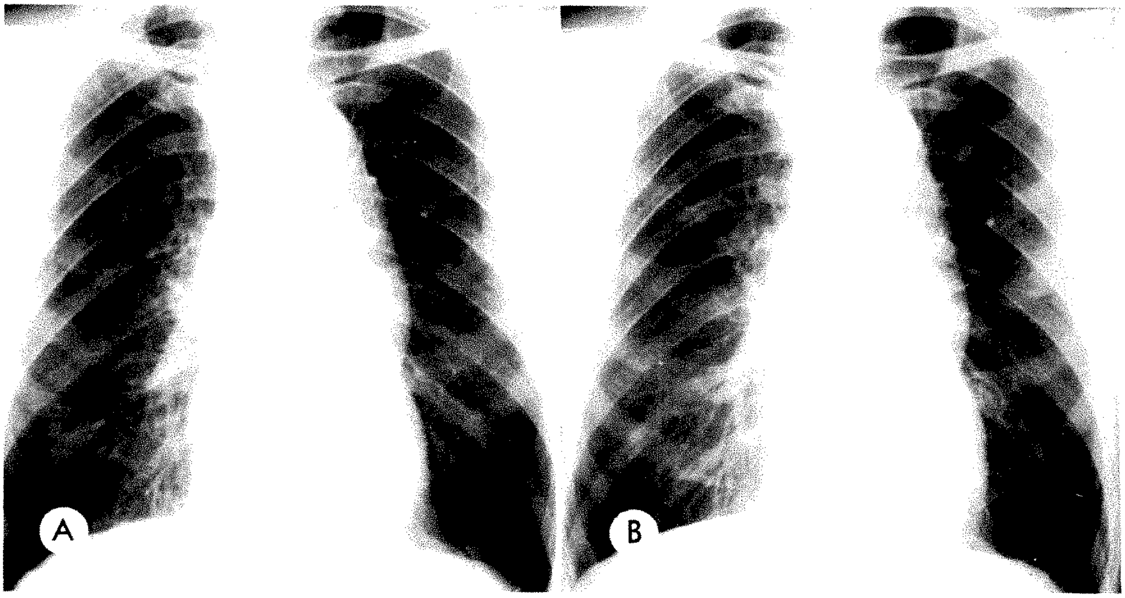

Fig. 4. (*A* and *B*) Response of a 62 year old male with hypertension, and a history and electrocardiographic findings of coronary insufficiency. Observe the diminution in size of the heart, pulmonary vessels and even the aorta, despite dilatation and extensive calcific sclerosis.

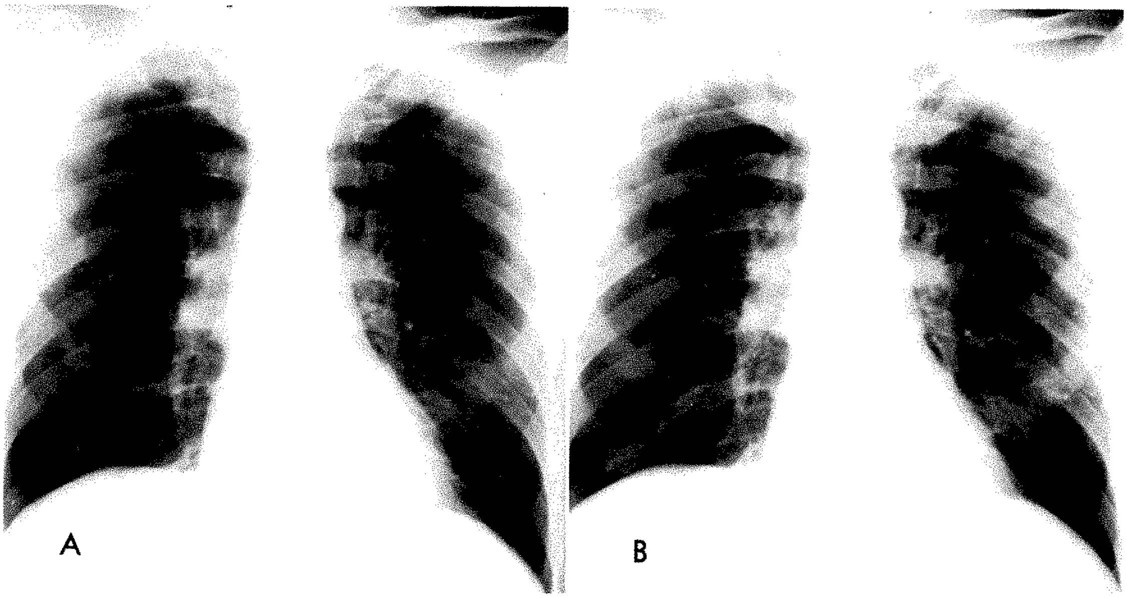

Fig. 5. (*A* and *B*) Improved demonstration of minimal hilar lymphadenopathy in a 66 year old male with chronic lymphocytic leukemia.

shunts without hypertension, and in combined pulmonary stenosis and intra-atrial septal defects (Fig. 12, *A* and *B*).

DISCUSSION

In light of more recent investigations, Westermark's hypothesis that "there is a fairly constant relation between the blood pressure in the pulmonary artery and the amount of intra-alveolar pressure required to compress the central branches" is an oversimplification. In intra-atrial septal defects with large left to right shunts and in severe pulmonary valvular stenosis with

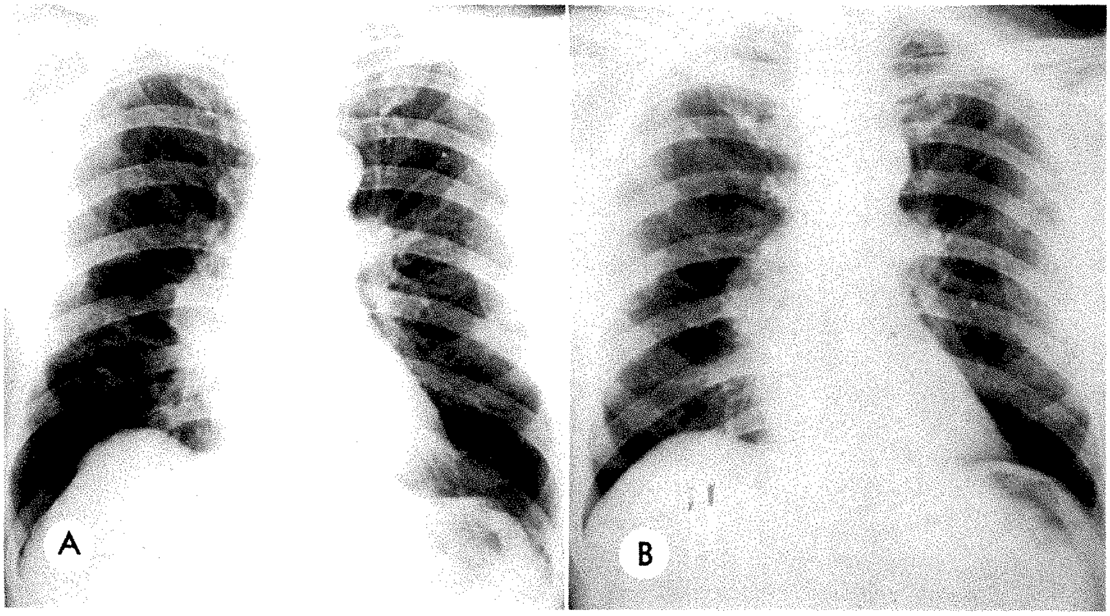

Fig. 6. (*A* and *B*) Oat cell carcinoma of the right main stem bronchus in a 61 year old male. Note the improvement in delineation of the obvious mass of the right hilus with this technique.

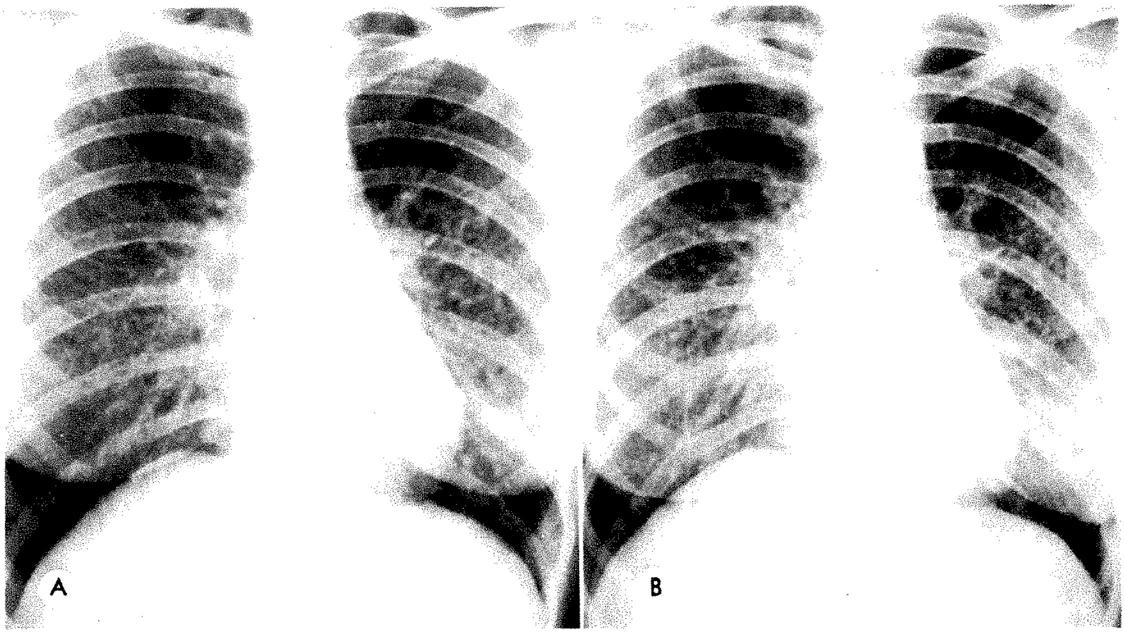

Fig. 7. (*A* and *B*) Sarcoidosis in a 31 year old female verified with lymph node biopsy. The Valsalva maneuver sharpens the definition of the pulmonary nodules and accentuates the linear shadows of fibrosis present.

normal or low pulmonary artery pressures, the Valsalva maneuver does not cause a diminishing of the size of the main pulmonary artery or of the "central branches."

From the exceptions to Westermark's hypothesis and the present day proposed mechanism of action in normal individuals, it is probable that the lack of effect of in-

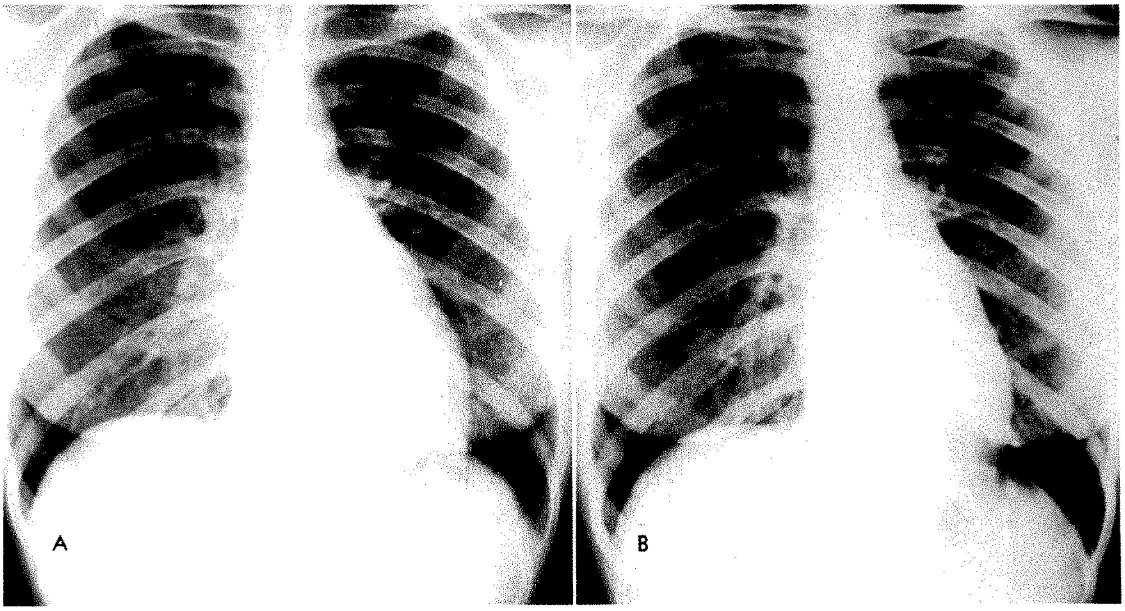

Fig. 8. (*A* and *B*) Twenty-three year old female with classic uncomplicated mitral stenosis. At valvulotomy, the valve opening was estimated to be 1.2 sq. cm. There is a diminution in the size of the heart and great vessels with the maneuver. Note the persistent convexity in the region of the left atrial appendage.

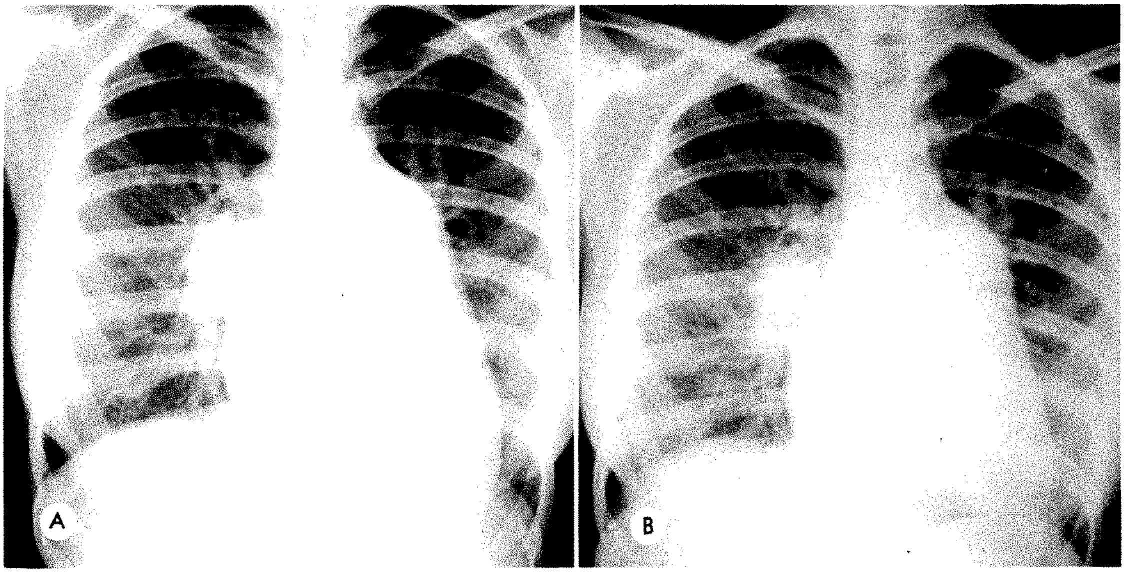

Fig. 9. (*A* and *B*) Proven pure mitral stenosis complicated by pulmonary hypertension. Pulmonary artery pressure was 70/50 mm. Hg. Calculated arteriolar resistance was 539 dynes sec./cm.$^{-5}$. Note the diminution in the heart size but lack of change in the appearance of the pulmonary vasculature.

creased intrabronchial pressure in the presence of pulmonary hypertension is mediated indirectly via an increased volume (and decreased compliance) of the right heart and central venous reservoir. The range of pressure and time employed in the examination as described is not sufficient to lower the effective filling pressure of the right heart. The increased pulmonary blood volume present with large intraatrial septal defects has been proposed as a factor in the lack of normal pressure and pulse responses to the Valsalva maneuver in this condition,[8] and may play some role

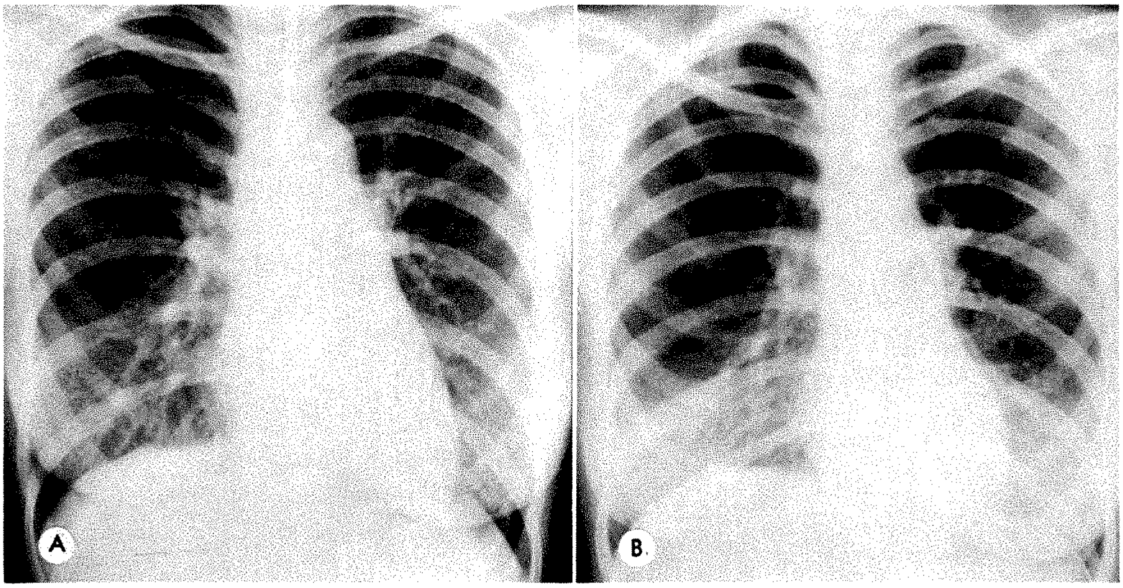

Fig. 10. (*A* and *B*) Proven uncomplicated patent ductus arteriosus. Note the diminution in size of heart, aorta and pulmonary vasculature to normal levels.

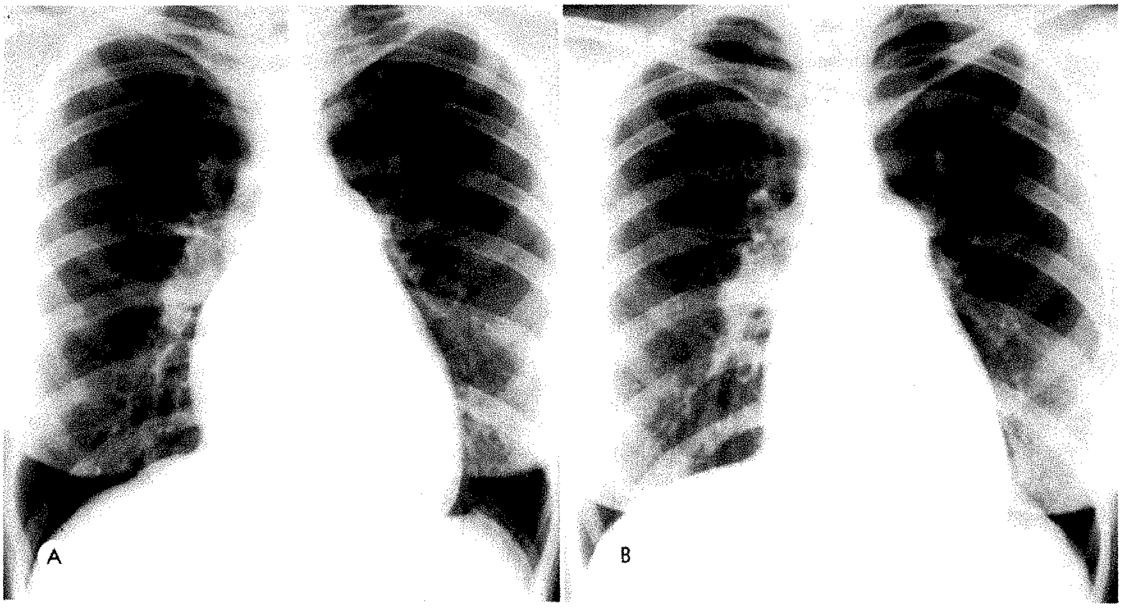

Fig. 11. (*A* and *B*) Thirty-seven year old female with slight digital clubbing, shortness of breath and cyanosis on exertion on the basis of primary pulmonary hypertension. The pulmonary artery pressure was 73/26 mm. Hg. The changes of pulmonary hypertension in the pulmonary vascular tree are not affected by the procedure.

in the apparent lack of diminution in the size of the pulmonary arterial tree as seen on roentgenograms.

One use proposed for this procedure is assumed to differentiate pulmonary arteriovenous fistula from solid tumors of the lung. A proven case of a large arteriovenous malformation was encountered in our series; however, the Valsalva maneuver did not appreciably diminish the size of the

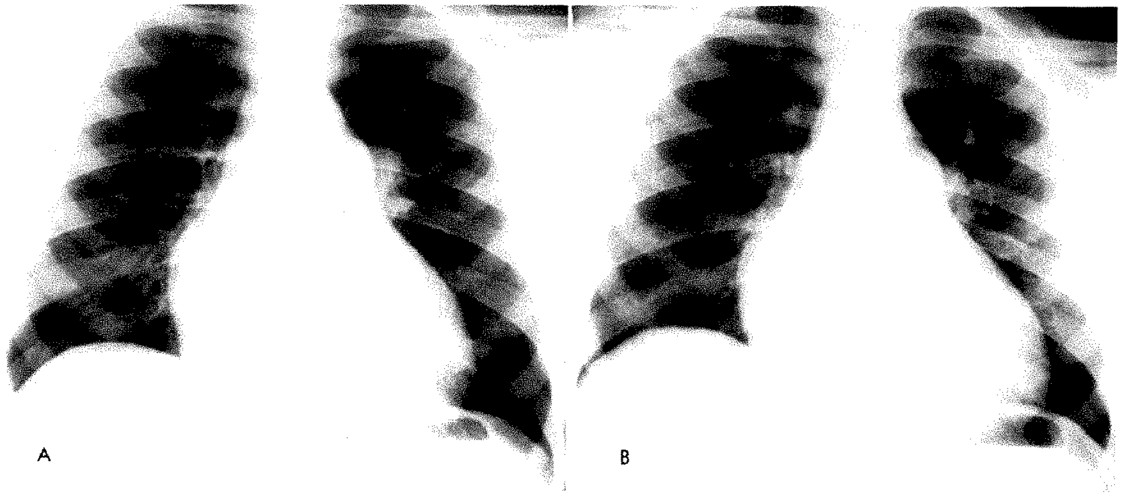

Fig. 12. (*A* and *B*) Nineteen year old white male with slight cyanosis since birth. Right ventricular pressure of 205/10 mm. Hg. Mean pulmonary artery pressure was 10 mm. Hg with 20 dynes/sec./cm.-5 pulmonary resistance. At surgery, tight pulmonary valvular stenosis with a 3 cm. ostium secundum atrial septal defect was present. Note the lack of change in the appearance of the dilated main pulmonary arterial tree with positive pressure despite the low pulmonary resistance.

mass with an adequate study. The explanation of this failure is unknown. It is possible that the wall of the abnormal vascular structure contained enough resilience due to fibrous tissue to keep it from collapsing despite a diminution in the internal pressure, or that the pressure-flow relationships were not significantly altered

Two other assumed uses of this procedure which we have not encountered are (1) in the diagnosis of constrictive pericarditis where there should be a lack of diminution in the size of the cardiopericardial silhouette and (2) in the diagnosis of pericardial effusion where the Valsalva maneuver is supposed to diminish the heart size and to accentuate the "water bottle" appearance of the cardiopericardial silhouette.

CONCLUSION

The Valsalva maneuver offers the radiologist an opportunity without the use of special equipment or a painful procedure to examine the heart and great vessels of an individual during an altered hemodynamic state. With only a mercury manometer salvaged from an old sphygmomanometer, a watch with a sweep second hand and a few instructions, the procedure can be carried out at the technical level.

In patients with a normal cardiovascular system, the procedure can be valuable in that it improves the visualization of selected pulmonary and hilar lesions by diminishing the size of the heart, aorta and pulmonary vessels. In patients with cardiovascular disease, the procedure can be used to estimate the effectiveness of a semi-standardized positive pressure effort in lowering the effective filling pressure of the heart. The response of the heart and vascular structures as seen roentgenographically can help establish the diagnosis of and/or judge the severity of a number of cardiovascular abnormalities.

SUMMARY

The Valsalva maneuver has been investigated in almost all of the disciplines of medicine during its 250 year history. A small part of this history is discussed with particular emphasis on the usefulness of the procedure in conjunction with plain and special roentgenography. Its value in plain roentgenography of selected cases of pulmonary disease is outlined and illustrated. Some of the more recent clinical and basic cardiovascular investigations are described and application of these concepts to plain roentgenography of the heart and great vessels is presented.

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SELECTIVE DILATATION OF THE RIGHT ATRIUM IN PREGNANCY*

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IN THIS report, we wish to describe an apparently unreported, normal variation in contour of the heart which appears in pregnancy; namely, selective dilatation of the right atrium. This dilatation may be sufficiently striking to suggest the presence of organic heart disease to those who are not aware of the nonpathologic nature of this roentgenographic finding.

MATERIAL

Radiologists are familiar with the increase in transverse diameter of the heart which occurs in pregnancy, even in the absence of significant diaphragmatic elevation. These changes have been well documented by many writers including Rollins and Bonte,[2] who also indicate that in the normal pregnant woman, the cardiac contour retains a normal configuration. The cardiac configuration which is usually seen in pregnancy is demonstrated in Figure 1, *A* and *B*. In contrast to this usual appearance, we have observed 38 pregnant women in the past 4 years who demonstrated apparent selective dilatation of the right atrium. In several of these before we became aware of its significance, the magnitude of this dilatation was sufficient to suggest organic heart disease.

Figure 2, *A* and *B* demonstrates the most marked example of right atrial dilatation in our series. This patient, a 21 year old Negro woman, was 6 months pregnant when first seen, and had no history of heart disease. Physical examination, electrocardiography, and cardiac catheterization demonstrated no organic lesion to explain this degree of atrial dilatation. Follow-up roentgenograms made 6 months later showed a decrease of total cardiac size, but persistence of the right atrial dilatation. Persistence of this dilatation to some degree has been true in several other women with right atrial dila-

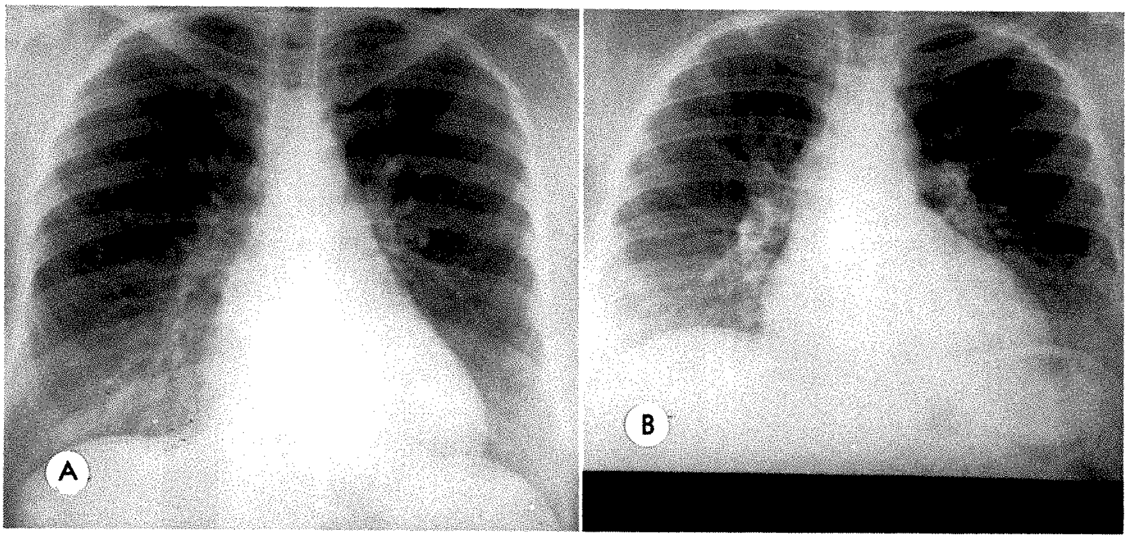

Fig. 1. (*A* and *B*) Frontal chest roentgenograms of 2 pregnant women showing fullness of the cardiac silhouette commonly seen in pregnancy.

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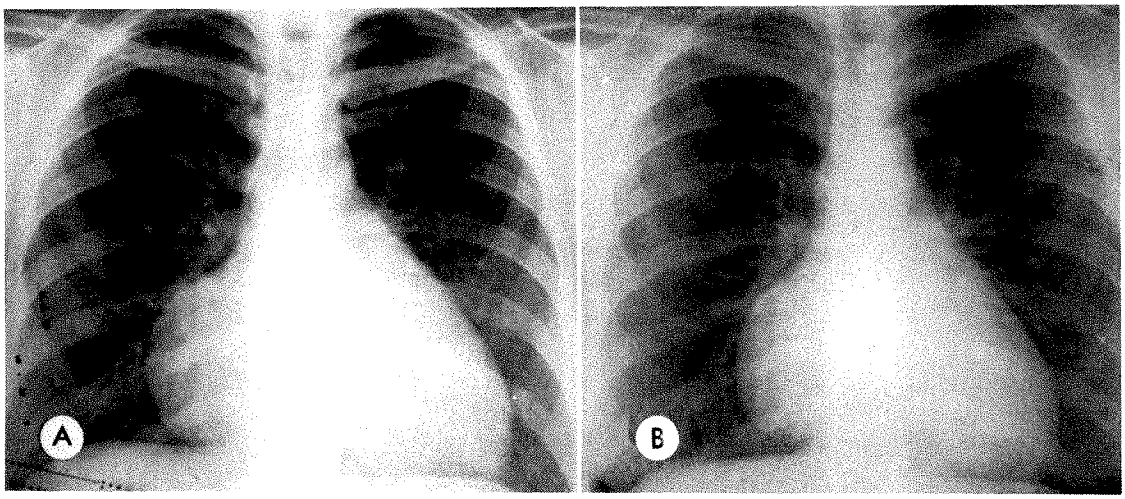

Fig. 2. Frontal roentgenograms showing the most marked example of right atrial dilatation found in this series and persistence of this dilatation after delivery. (*A*) Six months pregnant; (*B*) 6 months post partum.

tation, whom we have been able to follow roentgenographically (Fig. 3, *A-F*). In another woman, the atrial dilatation disappeared 2 days post partum. In all these women, the cardiac silhouette to the left of the spine has appeared normal in size and configuration, the dilatation of the right atrium being the only apparent aberration.

Figure 4, *A*, *B* and *C* shows the chest roentgenograms of 3 additional pregnant women and demonstrates the various degrees of right atrial dilatation which may be seen. None of these women presented any clinical signs or symptoms of heart disease on physical examination. In addition to the cardiac catheterization mentioned previously, we performed detailed cardiac work-ups, including electrocardiography, on 3 other of these women without finding any abnormality. The striking similarity in the roentgenographic appearance of these women has led us to attempt to diagnose, with a fair degree of success, pregnancy from the chest roentgenograms showing this finding.

COMMENT

Idiopathic dilatation of the right atrium is a poorly documented entity. Our review of the literature has shown only one article on this subject.[1] None of the reported women was pregnant. It is our premise that dilatation of the right atrium in the pregnant subject results from either or both of two physiologic variables; namely, elevation of right atrial pressures with resulting dilatation or adaptation to an increased blood flow. Although an increase in blood volume and cardiac output during pregnancy is known to occur, this would not seem to explain the degree of atrial dilatation which we have observed, since other conditions which result in sustained elevation of the cardiac output have not been associated with such changes to our knowledge.

Although we cannot, as yet, present a satisfactory explanation for such selective chamber enlargement, the fact that we do not see similar changes in many nonpregnant young women whom we survey routinely in our hospital would suggest that such dilatation occurs as a physiologic response to pregnancy. Our series includes one woman in whom we were able to observe the development of right atrial dilatation during her pregnancy. Our experience with this entity indicates that the elevation of the diaphragm seen in pregnancy does not provide an adequate explanation for this roentgenographic appearance, since such elevation was not evident in many of

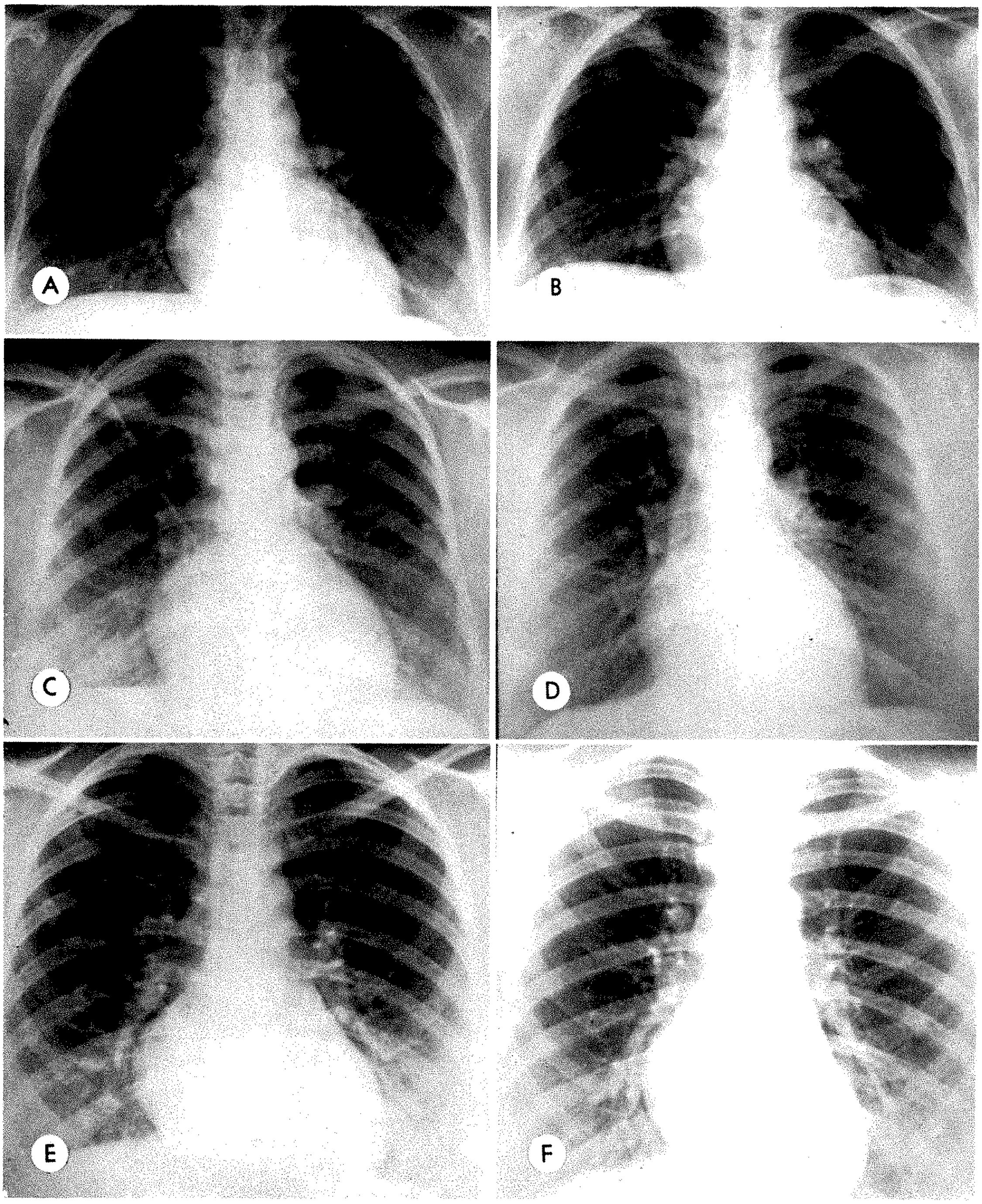

Fig. 3. Frontal roentgenograms of 3 pregnant women with right atrial dilatation with evidence of persistence of this dilatation in the postpartum period. (*A*) Six months pregnant; (*B*) 2 months post partum. (*C*) Eight months pregnant; (*D*) 1 year, 8 months post partum. (*E*) Four months pregnant; (*F*) 1 year, 5 months post partum.

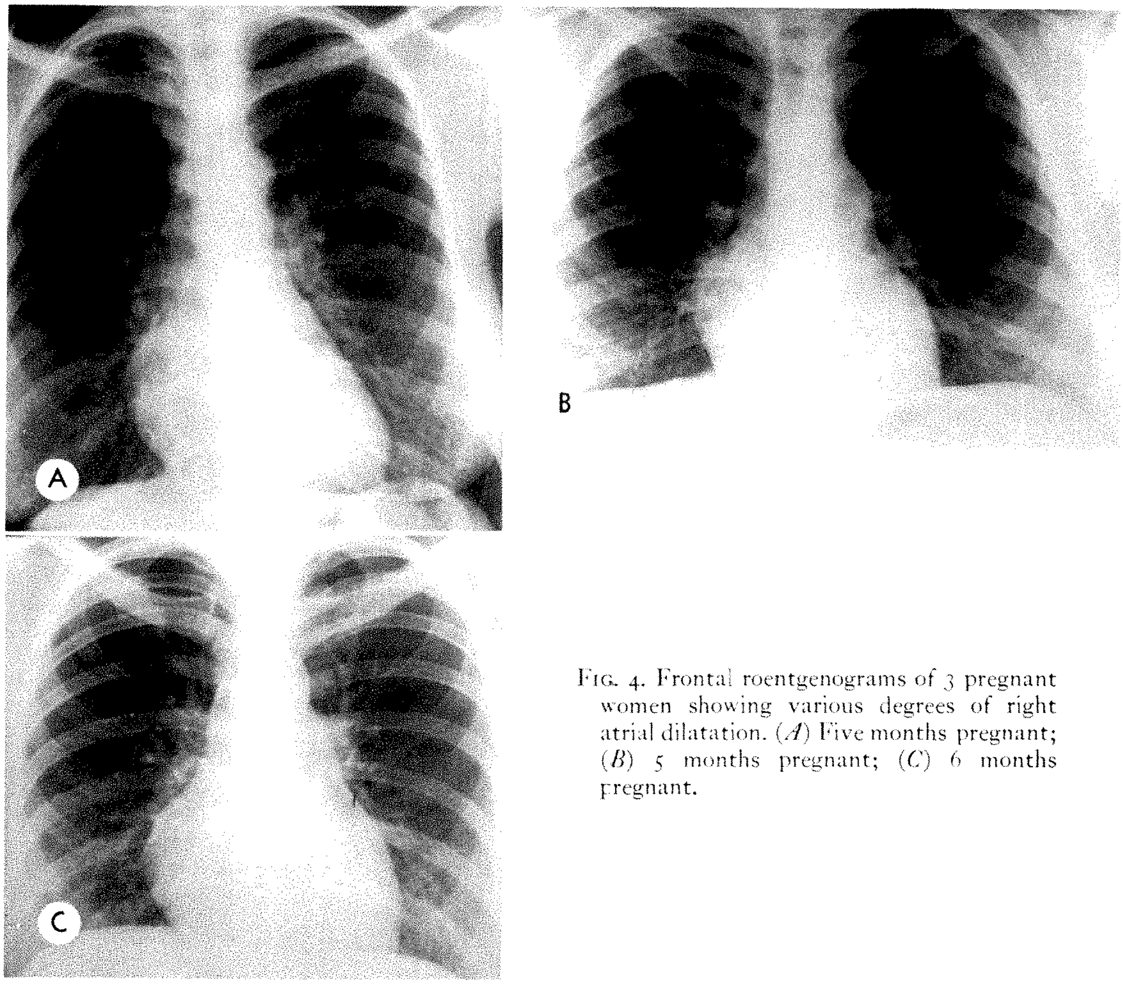

FIG. 4. Frontal roentgenograms of 3 pregnant women showing various degrees of right atrial dilatation. (*A*) Five months pregnant; (*B*) 5 months pregnant; (*C*) 6 months pregnant.

these women. We believe that it is important to recognize that right atrial dilatation in pregnancy is a normal variation which is apparently of no clinical significance. Such recognition will obviate the necessity for further investigation of this condition in the pregnant woman, thus preventing unwarranted anxiety and radiation exposure.

SUMMARY

Selective dilatation of the right atrium may occur as a normal variation of pregnancy and may persist in the postpartum period. We believe that this alteration in cardiac contour is of no clinical importance and should not lead to further clinical investigation.

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ROENTGEN FEATURES OF THE ATRIAL APPENDAGES*

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THE anatomic and roentgenologic features of the atrial appendages in health and disease were reviewed by studying a large number of angiocardiograms. This paper is an account of the findings with special attention to thrombosis of the left atrial appendage in rheumatic heart disease.

Embryologically, the right atrial appendage is formed from the right half of the primitive atrium and the left atrial appendage from the left half of the primitive atrium.[13] *Anatomically*, the left atrial appendage is longer and narrower than the right atrial appendage. It is directed forwards on the left side of the pulmonary artery and overlaps the root of this vessel. The right atrial appendage is a small conical muscular pouch with dentate margins. It projects from the upper and anterior portion of the sinus venarum forwards and towards the left side overlapping the root of the aorta.[11]

Roentgenologically, the exact location and size of the atrial appendages vary with atrial contraction; the atrial appendages are largest in atrial diastole.[18] The appendages are best visualized in the frontal view (Fig. 1, *A* and *B*). In the lateral projection, the right atrial appendage obscures the outflow tract of the right ventricle (Fig. 2*B*). The average normal size of the atrial appendages varies so much with atrial contraction that their measurements are impractical (Fig. 3, *A* and *B*).

CONGENITAL ANOMALIES OF THE ATRIAL APPENDAGES

Congenital atriomegaly is rare. Recently, Parmley[21] reported 2 patients with congenital atriomegaly owing to giant left atrial appendages. The first patient was an

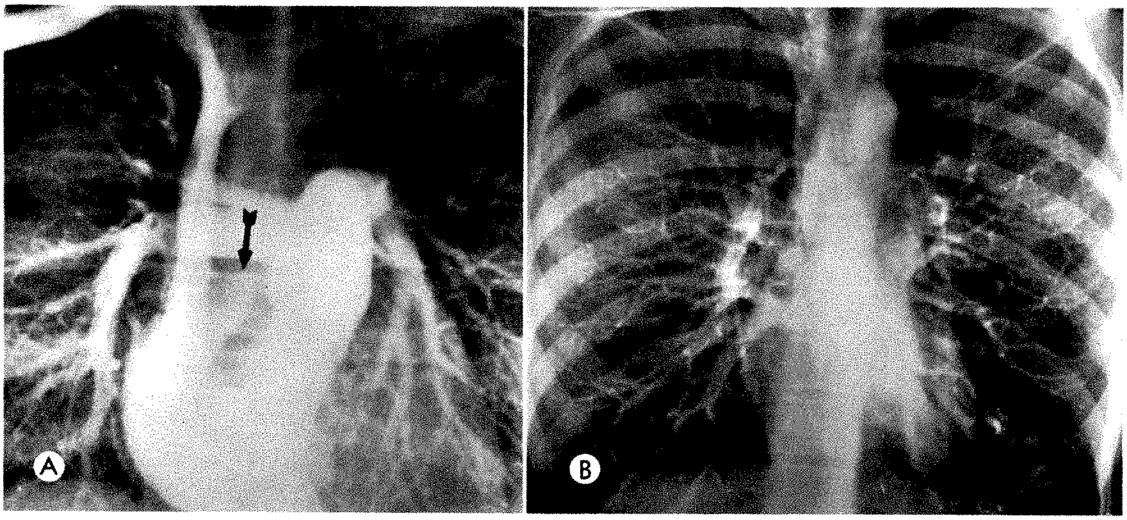

Fig. 1. *Normal atrial appendages.* (*A*) Frontal teleroentgenogram of a 16 year old girl showing the size, location, and appearance of the right atrial appendage (arrow). (*B*) Frontal teleroentgenogram of an 18 year old girl demonstrating the normal left atrial appendage.

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Aided by a grant from the Whitehall Foundation.
† Recipient of Investigatorship of The Health Research Council of The City of New York under contract No. I-258.

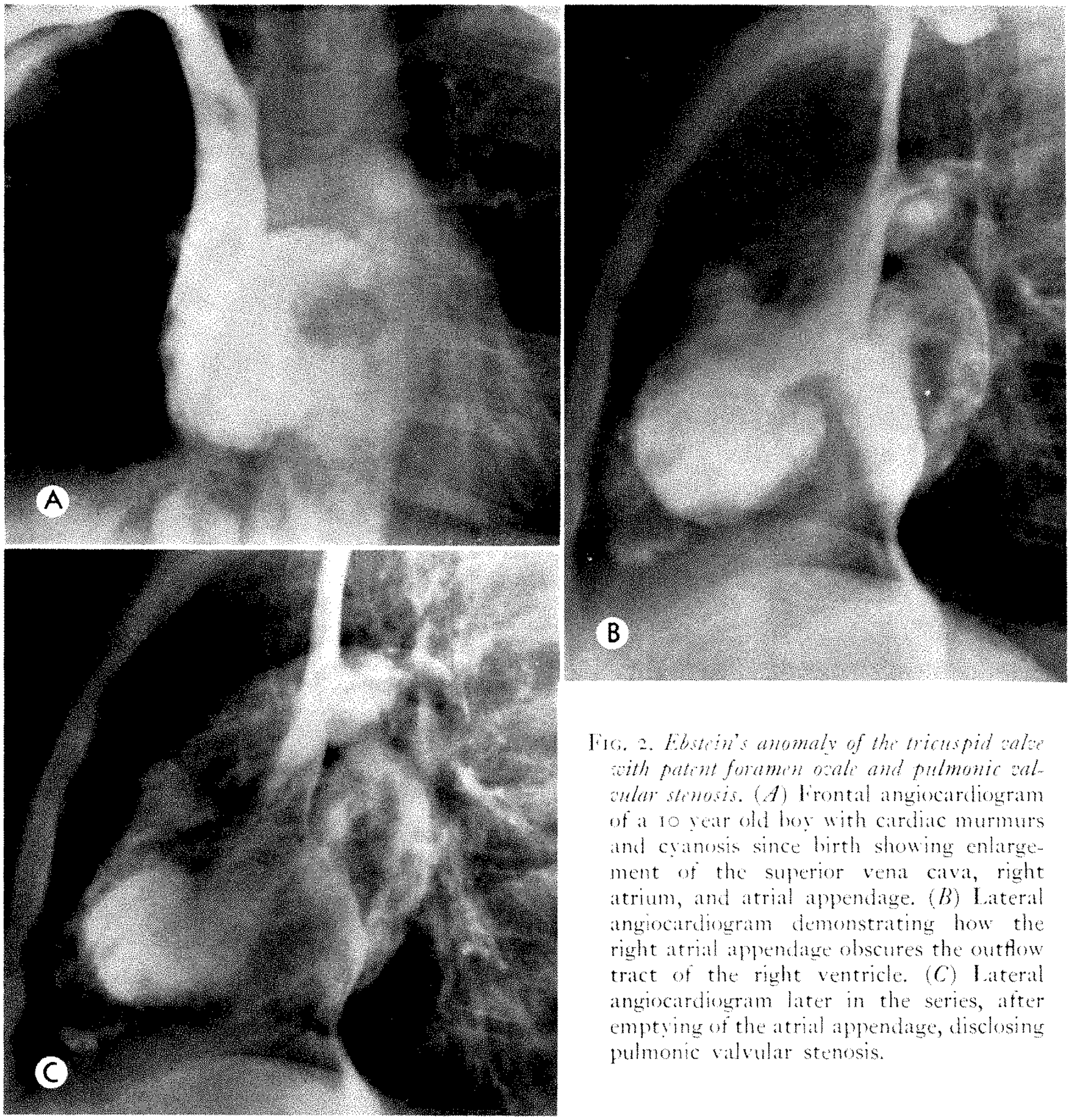


FIG. 2. *Ebstein's anomaly of the tricuspid valve with patent foramen ovale and pulmonic valvular stenosis.* (*A*) Frontal angiocardiogram of a 10 year old boy with cardiac murmurs and cyanosis since birth showing enlargement of the superior vena cava, right atrium, and atrial appendage. (*B*) Lateral angiocardiogram demonstrating how the right atrial appendage obscures the outflow tract of the right ventricle. (*C*) Lateral angiocardiogram later in the series, after emptying of the atrial appendage, disclosing pulmonic valvular stenosis.

11 year old boy with a left atrial appendage which measured 20 cm. in diameter at thoracotomy. The second case also had a large atrial appendage. In congenital mitral stenosis, the left atrium may be normal or enlarged.[6] Bernstein and colleagues reported a case with a small sized left atrial appendage;[3] however, in our experience the left atrial appendage in congenital mitral stenosis is usually enlarged (Fig. 4).

The right atrial appendage is very often enlarged in patients with pulmonic stenosis (Fig. 5, *A* and *B*), tricuspid atresia (Fig. 6*A*), and Ebstein's anomaly of the tricuspid valve (Fig. 2, *A*, *B* and *C*). In tricuspid atresia the left atrial appendage may also be very large (Fig. 6, *B* and *C*; and 7). Figure 8, *A* and *B* shows a patient with an enlarged right atrial appendage, transposition of the great vessels, and pulmonary atresia.

Lateroposition of the atrial appendages

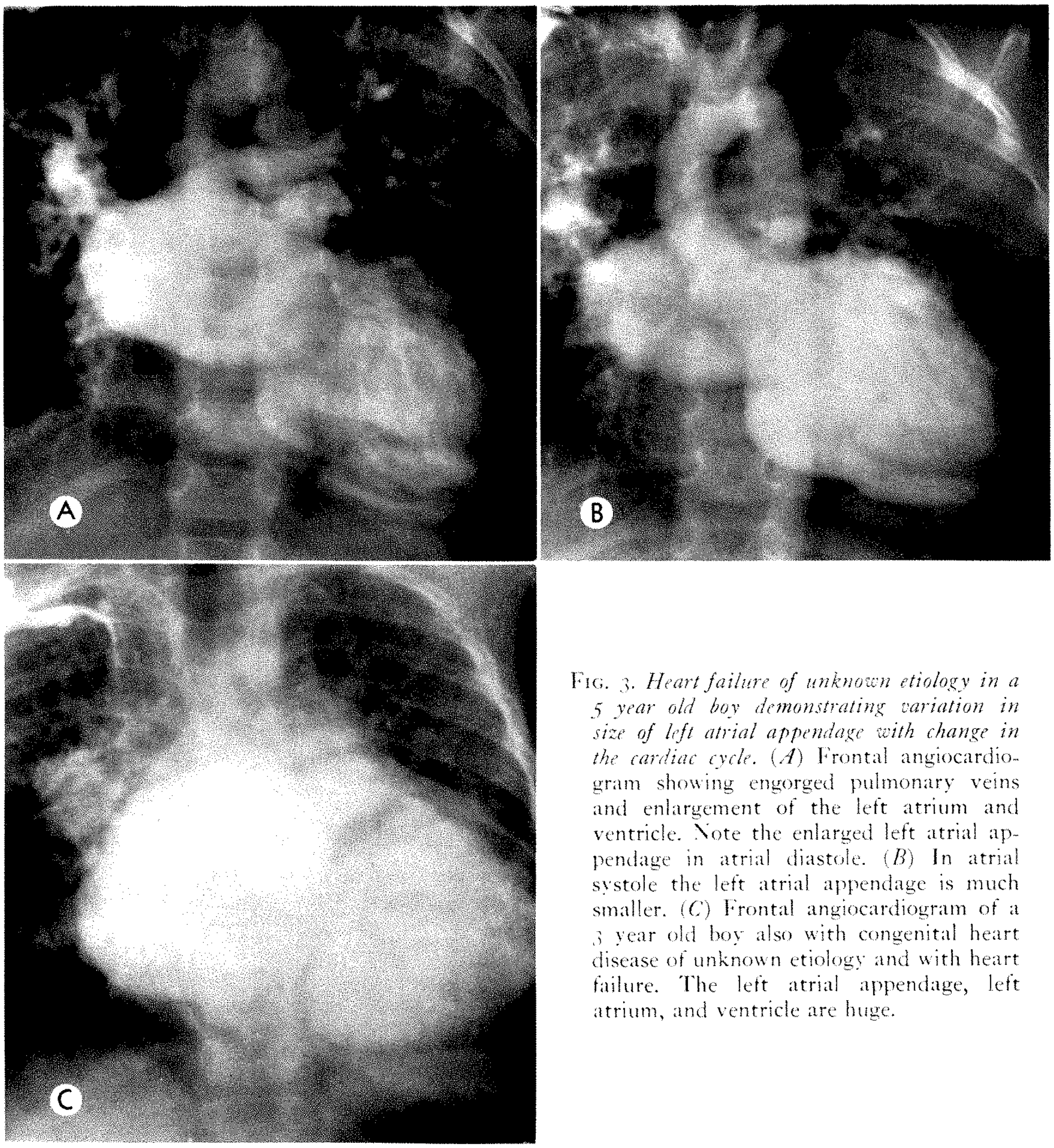


Fig. 3. *Heart failure of unknown etiology in a 5 year old boy demonstrating variation in size of left atrial appendage with change in the cardiac cycle.* (*A*) Frontal angiocardiogram showing engorged pulmonary veins and enlargement of the left atrium and ventricle. Note the enlarged left atrial appendage in atrial diastole. (*B*) In atrial systole the left atrial appendage is much smaller. (*C*) Frontal angiocardiogram of a 3 year old boy also with congenital heart disease of unknown etiology and with heart failure. The left atrial appendage, left atrium, and ventricle are huge.

is an uncommon congenital anomaly and refers to a developmental abnormality associated with transposition of the great vessels. Both appendages lie side by side either on the left or right side of the heart. Smyth[23] reported a case and reviewed the literature and out of a total of 18 patients found that the atrial appendages were located on the left side of the heart in 16 instances and on the right side in 2. Recently, Fragoyannis and Nickerson[8] reported a single case in which the patient had both appendages on the left side. The cardiac lesions in this instance consisted of aortic and tricuspid atresia. They proposed the term juxtaposition rather than lateroposition of the atrial appendages.

An unusual case of partial absence of the pericardium with herniation of the left atrial appendage simulating mediastinal

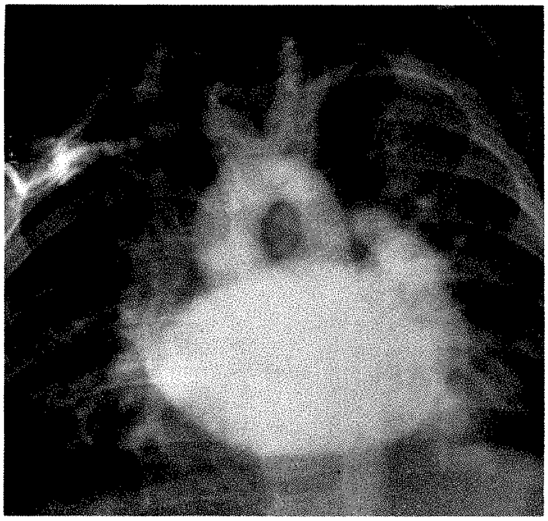


Fig. 4. *Frontal angiocardiogram of congenital mitral stenosis in a 21 month old infant.* The left atrium and appendage are markedly enlarged.

tumor was seen at The New York Hospital and is deemed worthy of mention.

REPORT OF A CASE

A 43 year old Caucasian woman (N.Y.H. #845651) had an abnormal left heart silhouette in the region of the pulmonary artery. This was discovered during a routine chest survey 5 years prior to admission (Fig. 9*A*). Her complaint was pain in the left anterior chest and arm during exertion or emotion, which was aggravated in the supine position. The blood pressure was 130/70 mm. Hg and the pulse was 72 and regular. A faint systolic murmur was heard at the apex of the heart. The electrocardiogram was normal. A mass in the left hilus was visualized on a frontal roentgenogram.

An angiocardiogram on February 10, 1960, showed the opacified left atrial appendage to be the cause of the abnormal shadow in the left hilus (Fig. 9*B*). Thoracotomy by Dr. Laurence Miscall disclosed that the left atrial appendage was herniated through a partial defect in the left side of the pericardium. The pericardium was mobilized and, as the base of the left ventricle was approached, it was noted that absence of the pericardium extended from the anterior surface of the pulmonary artery to the left inferior pulmonary vein. The patient made an uneventful recovery and became asymptomatic following operation.

Comment. There are over 100 cases of congenital absence of the pericardium reported in the literature;[4,5,7,9,12,14-16,17,20] however, only 6 are recorded with left atrial appendage herniation.[4,14,16,17,20] The above case is 1 of 4 in which angiocardiography suggested that the abnormal left hilar silhouette was the left atrial appendage. Hering, Wilson, and Ball[14] described 2 cases

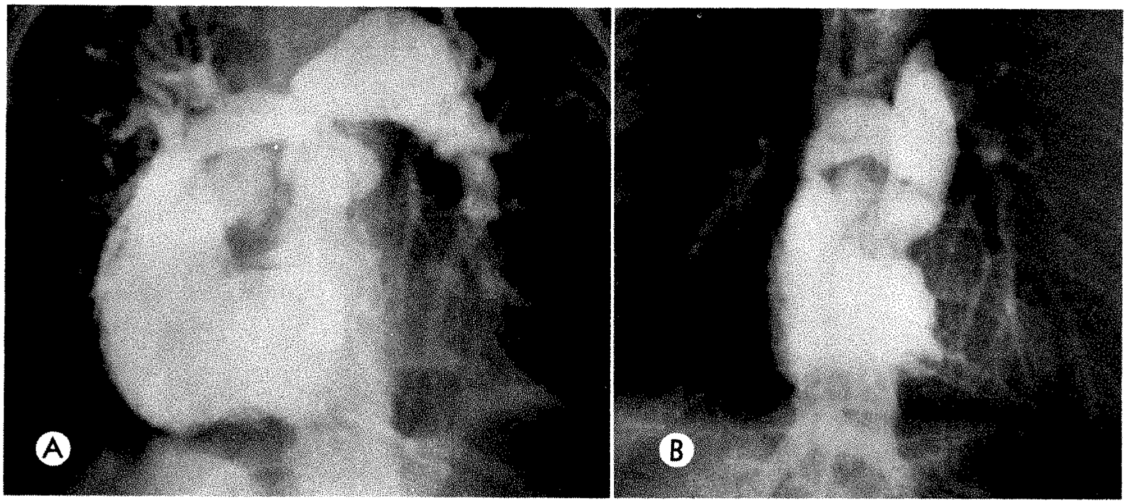


Fig. 5. *Congenital valvular pulmonic stenosis with enlargement of the right atrial appendage.* (*A*) Frontal angiocardiogram of a 6 year old child with a huge right atrial appendage. (*B*) Moderate enlargement of the right atrial appendage in a 27 year old woman.

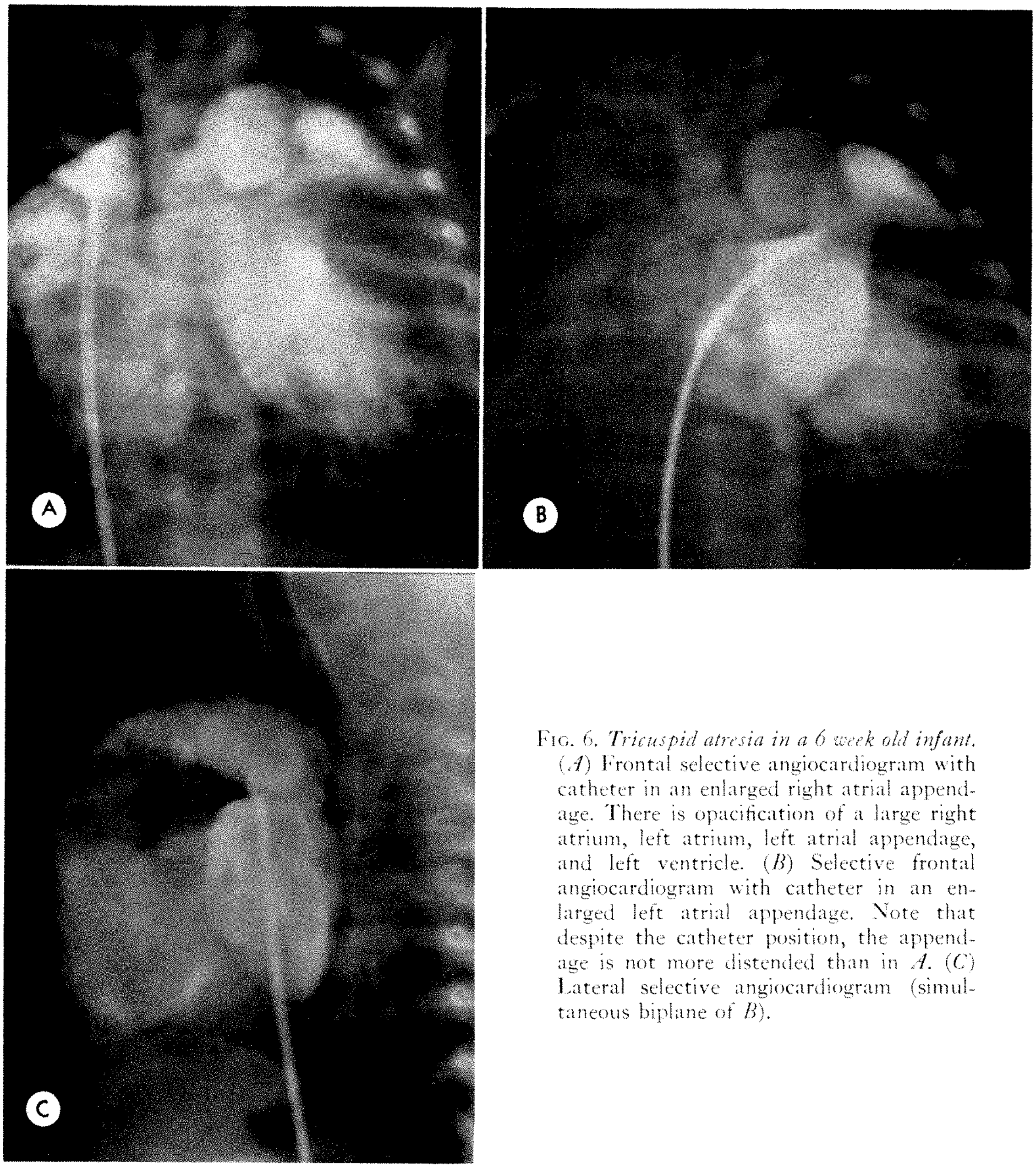


Fig. 6. *Tricuspid atresia in a 6 week old infant.* (*A*) Frontal selective angiocardiogram with catheter in an enlarged right atrial appendage. There is opacification of a large right atrium, left atrium, left atrial appendage, and left ventricle. (*B*) Selective frontal angiocardiogram with catheter in an enlarged left atrial appendage. Note that despite the catheter position, the appendage is not more distended than in *A*. (*C*) Lateral selective angiocardiogram (simultaneous biplane of *B*).

of congenital absence of the pericardium; in 1, the left atrial appendage was visualized angiocardiographically. The remaining 2 were reported by Fowler[7] and Kavanagh-Gray and associates,[16] respectively.

RHEUMATIC HEART DISEASE

Thrombus in the left atrial appendage is of considerable importance in rheumatic heart disease, for this finding will alter the surgeons approach to mitral valvulotomy. Indeed, Graef and colleagues,[10] in a review of thrombosis in rheumatic heart disease, found that the atrial appendages were involved in 84 per cent of the cases. In the other 16 per cent the thrombus was confined to the atrium without involving the appendages. Arendt and Cardon[1] reported that the demonstration of undue prominence of the left atrial appendage on the

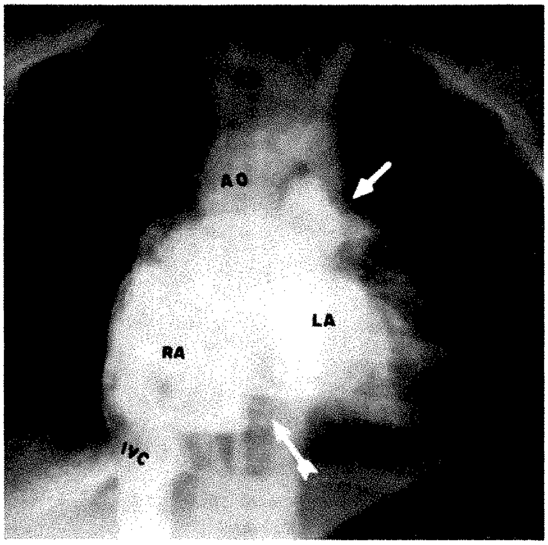


Fig. 7. *Frontal angiocardiogram in a 1½ year old child with tricuspid atresia.* Upper arrow points to the enlarged left atrial appendage. IVC is the inferior vena cava; RA, right atrium; LA, left atrium; AO aorta. Lower arrow points to hypoplastic unopacified right ventricle.

conventional roentgenogram was of value in the diagnosis of left atrial thrombosis. Calcification of the thrombus was described by Berk[2] as also a good sign of atrial thrombus. Since these signs are so uncommon, it seemed important to evaluate intravenous angiocardiography in the diagnosis of thrombus in the left atrial append-

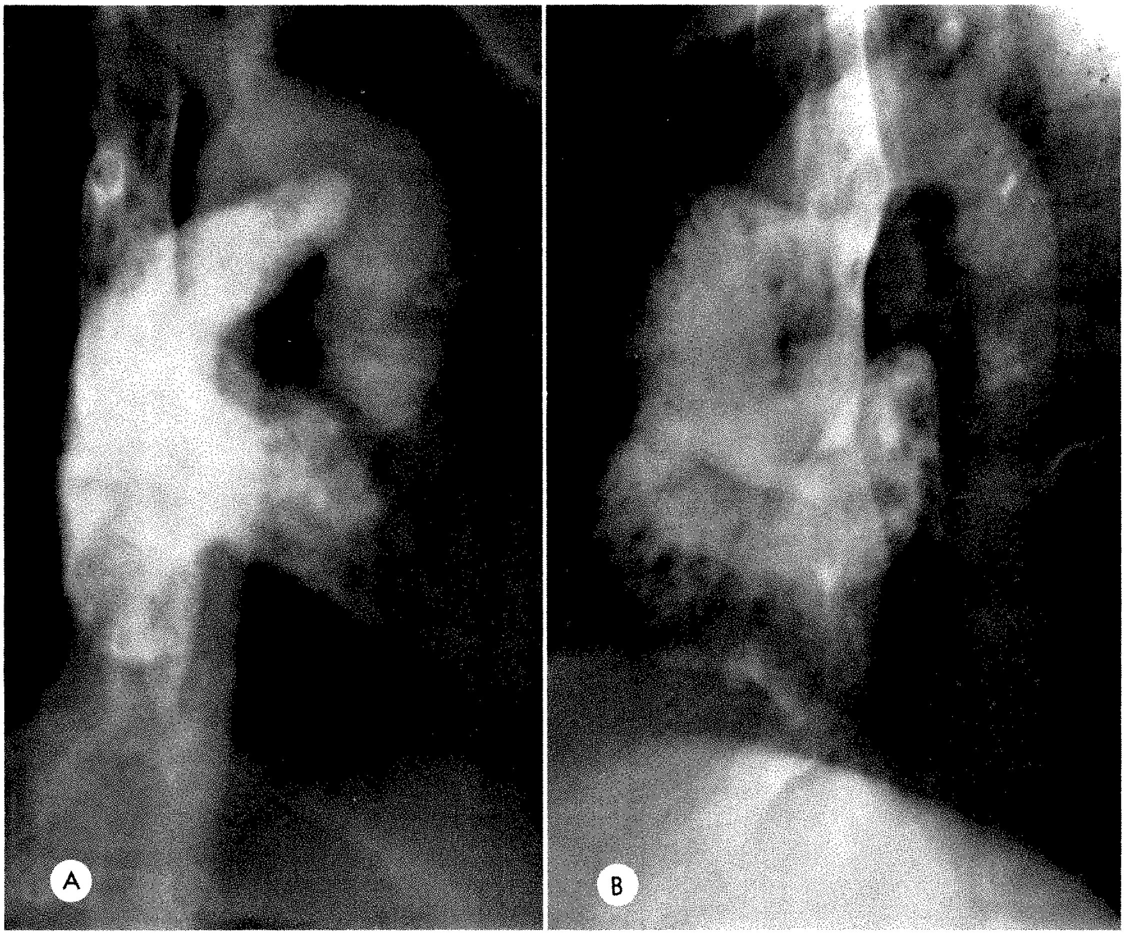


Fig. 8. *Huge right atrial appendage in a 2½ year old child with transposition of the great vessels and pulmonary atresia.* (*A*) Frontal intravenous angiocardiogram showing the huge right atrial appendage arising from the atrium; the large opacified aorta comes off the right ventricle. (*B*) Lateral (simultaneous biplane of *A*) angiocardiogram demonstrating how the enlarged right atrial appendage obscures the origin of the aorta.

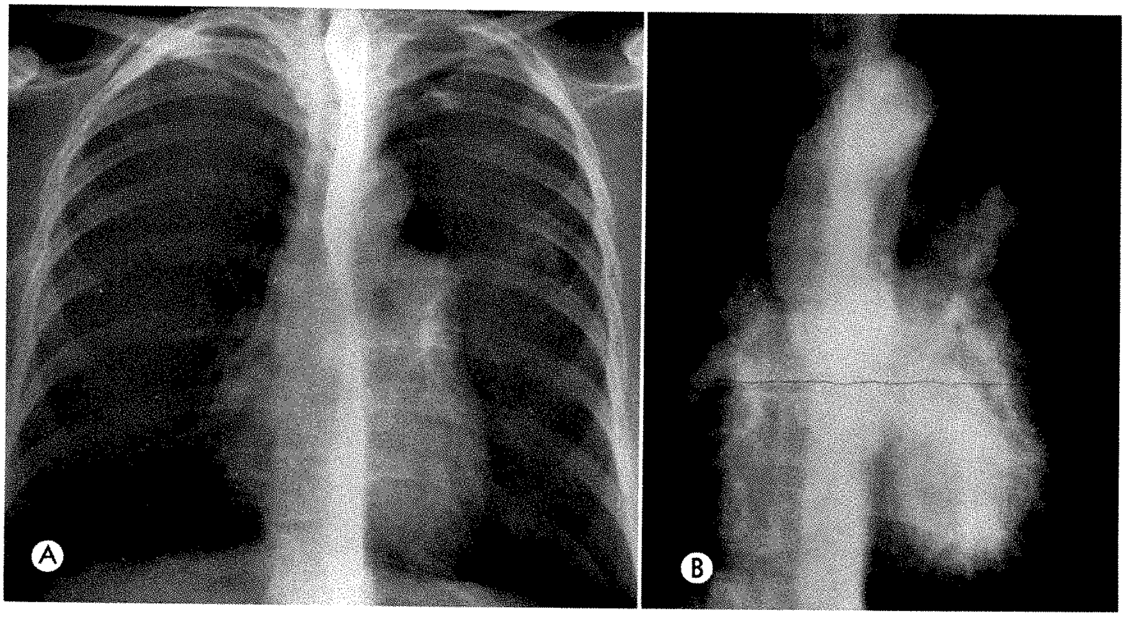


Fig. 9. *Herniation of the left atrial appendage through a congenital partial defect of the pericardium.* (*A*) Frontal teleroentgenogram showing a mass in the left hilus. (*B*) Angiocardiogram clearly demonstrates the left atrial appendage to be the mass.

age;[22,26] therefore, the angiocardiographic findings were correlated with the surgical and pathologic findings in 50 patients (Table I). In 36 patients without thrombus (72 per cent of the cases), the left atrial appendage was not visualized. Thus, failure to visualize the left atrial appendage on intravenous angiocardiograms does not necessarily mean that a formation of a clot has occurred. Of the 11 instances in which the left atrial appendage was visualized, only 1 patient had a thrombus, and this was seen only microscopically in the wall of the excised appendage. For practical purposes, if the atrial appendage is visualized, it may be assumed that no thrombus is present (Fig. 10, *A*, *B* and *C*; and 11). Atrial thrombi, however, are usually easily visualized.[19,24]

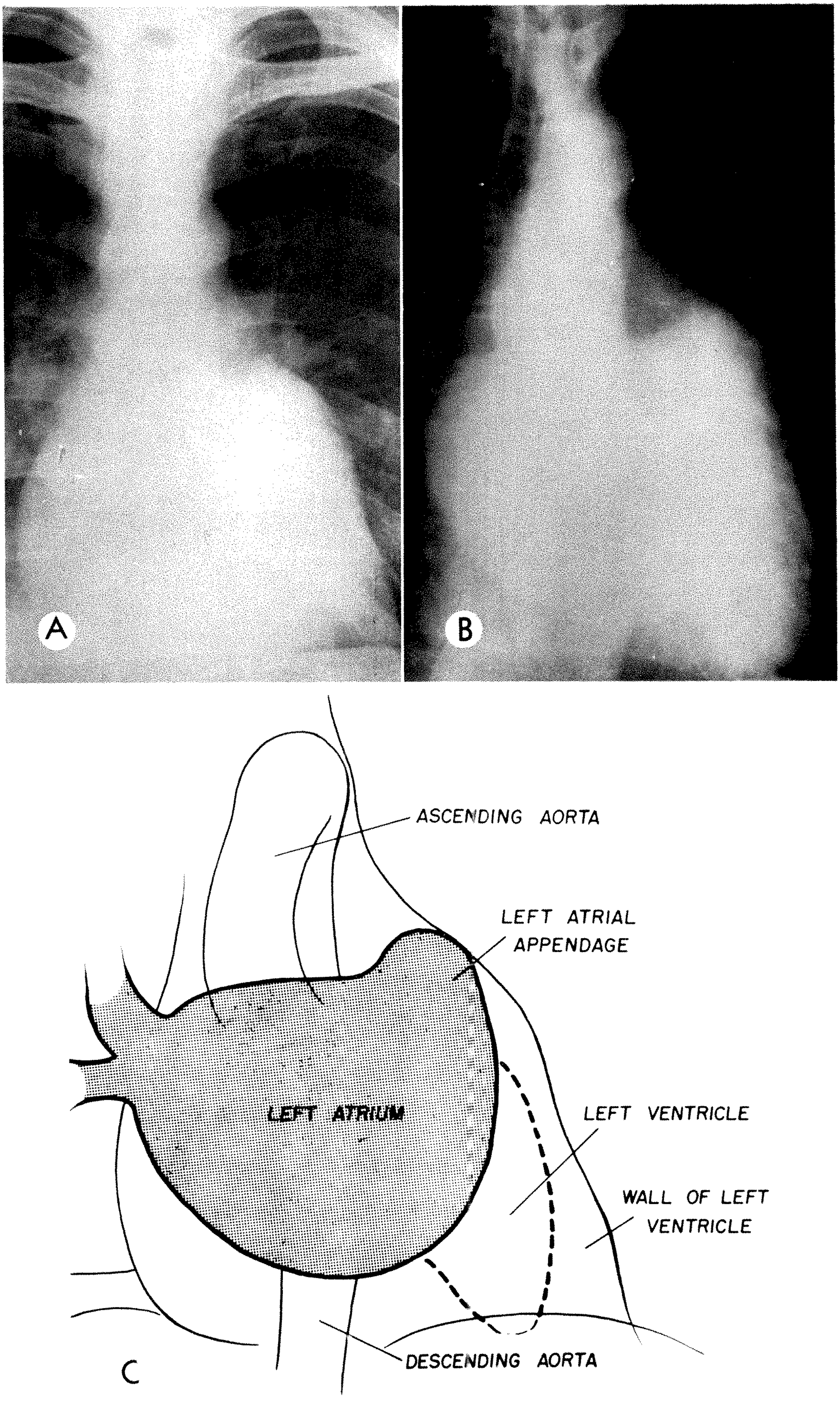
Recently, a 60 year old woman with rheumatic heart disease and mitral stenosis came to operation, and calcification of the left atrial appendage (Fig. 12) was verified. Because of obliteration of the left atrial appendage, the operative approach to the mitral valve was via the right border of the left atrium.

Studies of the left atrial appendage have been found useful in differential diagnosis. Jacobson and Weidner[15] reported that dilatation of the left atrial appendage following the Valsalva maneuver occurs in mitral stenosis and strongly recommended the maneuver for diagnosis. In a recent communication, Steinberg and associates[27] have reported that thrombosis of the left atrial appendage associated with filling defects in the left atrium was a reliable sign of an atrial

Table I

ATRIAL APPENDAGE VISUALIZATION IN ANGIOCARDIOGRAPHY OF 50 PATIENTS WITH RHEUMATIC MITRAL STENOSIS

Both atrial appendages visualized	0
Only right atrial appendage visualized	11
Only left atrial appendage visualized	11
Neither atrial appendage visualized	28
SURGICAL AND PATHOLOGIC FINDINGS (LEFT ATRIAL APPENDAGE)	
Thrombus in nonvisualized appendage	3
Thrombus with visualization of left atrial appendage	1


A
B
ASCENDING AORTA
LEFT ATRIAL APPENDAGE
LEFT ATRIUM
LEFT VENTRICLE
WALL OF LEFT VENTRICLE
DESCENDING AORTA
C

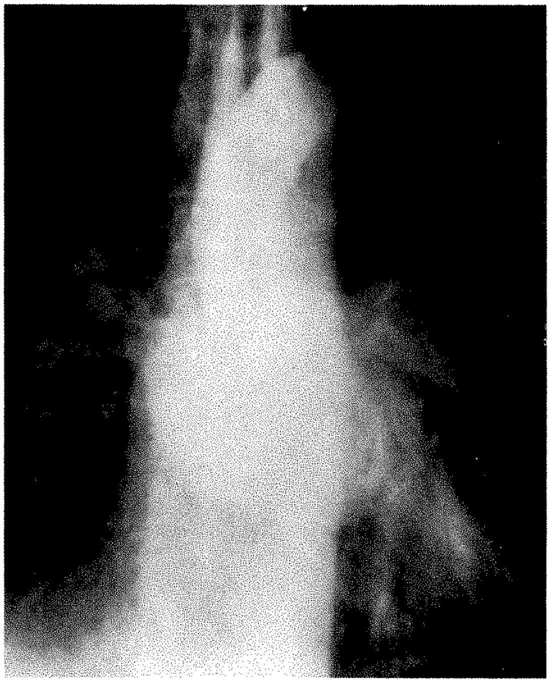


FIG. 11. Frontal angiocardiogram demonstrating a huge left atrial appendage in a 57 year old woman with rheumatic mitral stenosis. The left atrium is only slightly enlarged.

thrombus rather than of a myxoma.

A bullet trapped in the right atrial appendage was recently localized by angiocardiography.[25] It had found its way to the atrial appendage after a shrapnel injury to the left leg in World War I. It was removed in order to alleviate anxiety. Perforation of the atrial appendage may occur when selective angiocardiography is performed using a stiff catheter. Fortunately, this did not occur in the patient illustrated in Figure 6, *A*, *B*, and *C*.

SUMMARY AND CONCLUSIONS

Angiocardiography by visualizing the cardiovascular structures permitted the detailed roentgen study of the atrial appendages. Alterations of the atrial appendages in congenital and acquired heart disease were reviewed and academic and practical data concerning the atrial appendages were secured.

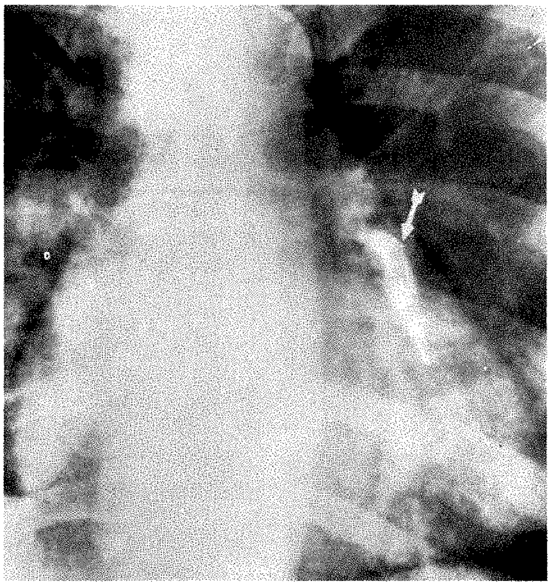


FIG. 12. Enlarged conventional frontal roentgenogram of a 60 year old woman with rheumatic heart disease and calcification of the left atrial appendage (arrow).

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FIG. 10. *Large left atrial appendage in a 45 year old man with rheumatic mitral stenosis.* (*A*) Frontal teleroentgenogram showing prominence of the left cardiac silhouette in the region of the left atrial appendage. (*B*) Frontal angiocardiogram showing the large unclotted atrium and appendage. (*C*) Tracing of *B*.

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TRICUSPID ATRESIA*

REPORT OF A CASE WITHOUT TRANSPOSITION OR PULMONARY STENOSIS

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Tricuspid atresia may be associated either with normally related or transposed great arterial vessels, and pulmonary stenosis may or may not be present.[3] The most common variety is that in which the great vessels are normally related and in which pulmonary stenosis and subpulmonary stenosis are associated.

In the most common variety the roentgenographic appearance is quite uniform from case to case. Usually, the heart is of normal size or slightly enlarged. There is often a convexity of the left cardiac border, and the pulmonary vascular markings are either diminished or at the lower limits of normal. In the uncommon form there is marked cardiomegaly and an obvious increase in pulmonary vascularity.

The case to be presented, being of an uncommon variety, concerns a patient in whom there was neither transposition of the great vessels nor pulmonary stenosis.

REPORT OF CASE

A 1 month old boy was admitted to the University of Minnesota Hospitals with a mild upper respiratory infection and cardiac failure. The infant had been slightly dusky for a week prior to admission, although no cyanosis had been noted at the time of his birth. The mother had been exposed to German measles during the second month of pregnancy at which time she had received gamma globulin.

Physical examination of the infant revealed a loud, harsh, systolic murmur at the lower left sternal border. The murmur, transmitting widely into the axilla and the back, was associated with a thrill. The liver was palpable 4 cm. below the right costal margin, and the spleen was slightly enlarged.

An electrocardiogram indicated the presence

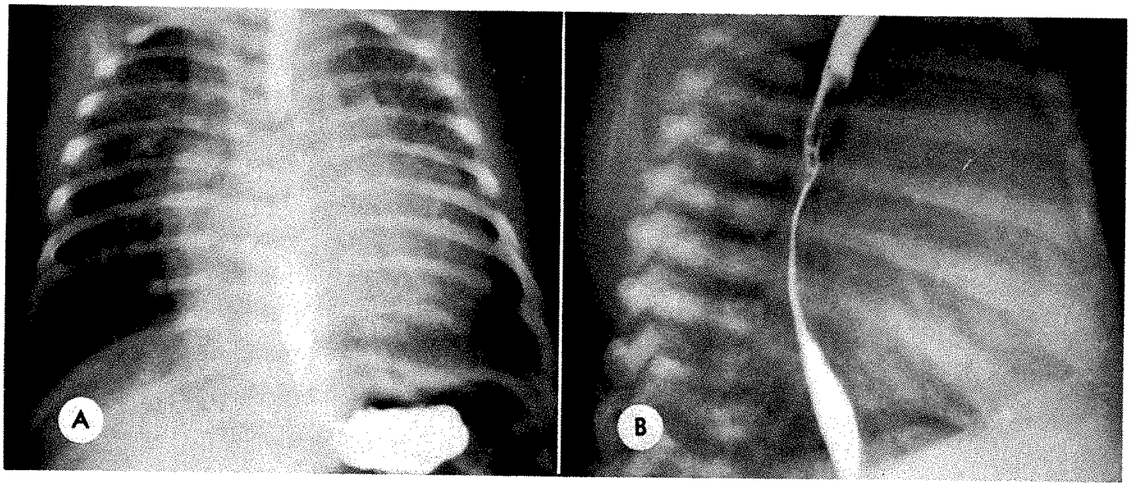

Fig. 1. (*A*) Frontal and (*B*) lateral roentgenograms of the thorax show marked cardiomegaly with increased pulmonary vasculature. In the lateral view there is an indentation of the anterior aspect of the barium-filled esophagus which is caused by enlargement of the left atrium.

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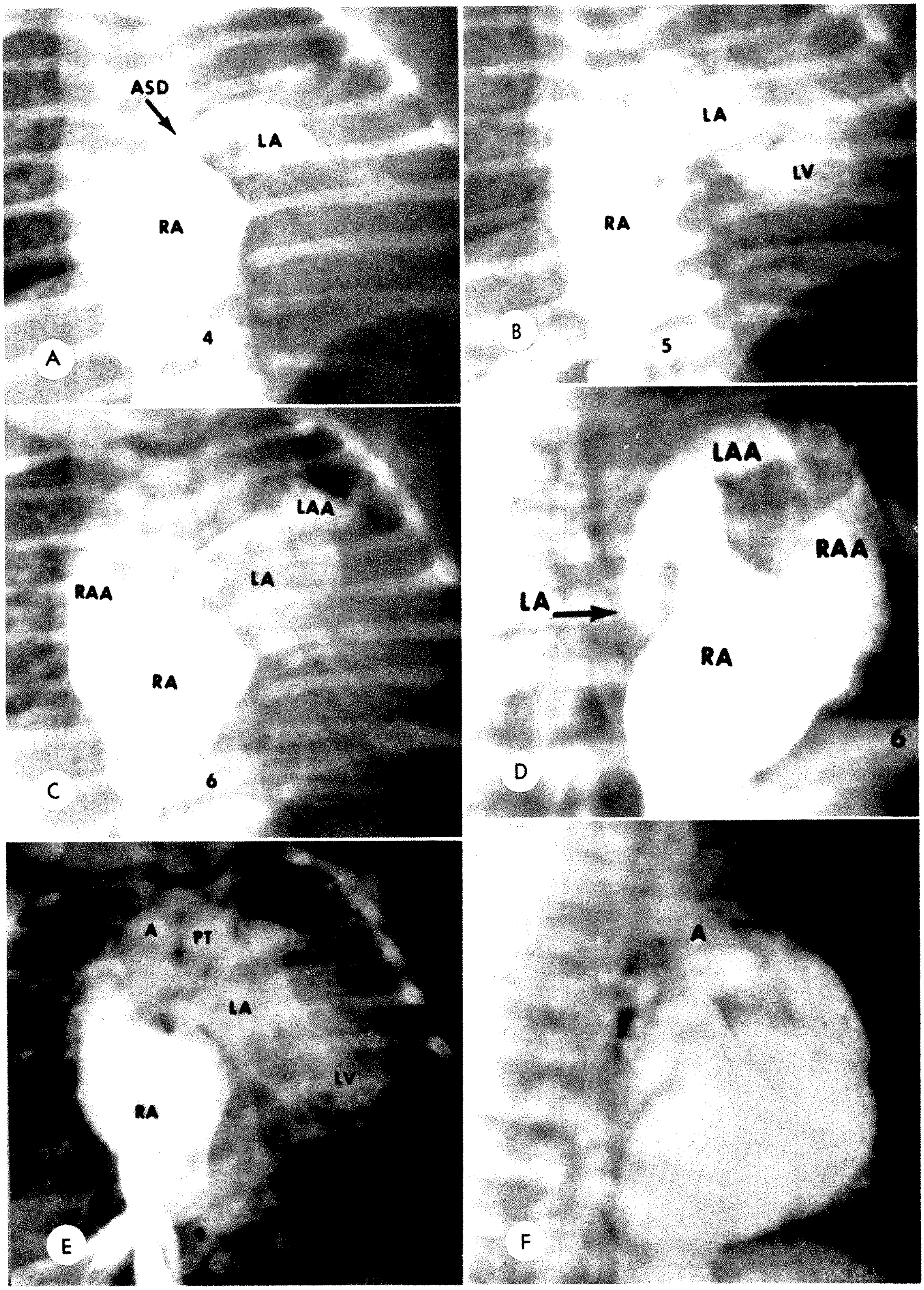
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of right atrial hypertrophy, left ventricular hypertrophy, and left axis deviation. In addition, it was thought that left atrial hypertrophy was also present.

Frontal and lateral roentgenograms of the thorax showed marked cardiomegaly and increased pulmonary vascularity. Left atrial enlargement was also present (Fig. 1, *A* and *B*). Forward angiocardiography was performed. These studies (Fig. 2, *A-F*) showed sequential opacification of the inferior vena cava, the right atrium, left atrium, the left ventricle and, subsequently, there was simultaneous opacification of both great vessels. In the lateral view the great vessels were normally interrelated. No ductus arteriosus was demonstrated. Contrast medium appeared to stream across the right atrium, through the patent foramen ovale, and into the left atrium. The left atrium filled densely and appeared to lie to the left of the normal position. No filling of a right ventricular chamber was detected. The diagnosis of tricuspid atresia and ventricular septal defect, with normal relationship of the great vessels, was made.

The child died shortly after returning home.

Pathologic Findings. Examination of the necropsy specimen revealed the great arterial vessels to be of about equal caliber and in correct interrelation. At the anticipated location of the tricuspid valve, there was neither an orifice nor was there valvular tissue (Fig. 3 and 4*A*). An atrial septal defect at the fossa ovalis was the route of exit for right atrial blood. The mitral valve led into a chamber resembling the left ventricle from which the aorta arose in a normal manner. A large ventricular septal defect, which lay below the aortic valve and anterior to the mitral valve, led into a large infundibular chamber (Fig. 4*B*). The latter was located at the anterior basal aspect of the ventricular mass and from its upper end the pulmonary trunk arose. Attached to the anterior leaflet of the mitral valve was a collection of accessory valvular tissue which, in turn,

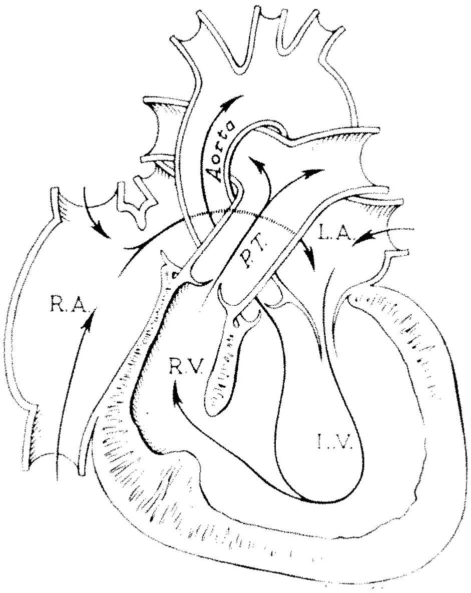

Fig. 3. Diagram showing the anatomic features of the heart and great vessels in the case reported (tricuspid atresia without transposition, wide ventricular septal defect, and near normally sized infundibular chamber).

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Fig. 2. Forward angiocardiograms. Exposure at the rate of 5 films per second. Numbers on individual films indicate their position in the sequence. (*A*) Contrast medium fills the right atrium (RA) and streams through the atrial septal defect (ASD) into the left atrial chamber (LA). (*B*) Progress of contrast medium from the left atrium into the left ventricle (LV). (*C* and *D*) Simultaneous frontal (*C*) and lateral (*D*) views. Contrast material has appeared in the aorta and pulmonary trunk but there is insufficient material in these vessels at this stage for them to be clearly outlined. Hazy area of increased density with a superior convex margin, represents the aorta which lies above the opacified right (RA) and left atrial (LA) chambers. RAA = right atrial appendage; LAA = left atrial appendage. (*E*) Frontal view. The aorta (A) and pulmonary trunk (PT) are now well defined, as is the enlarged left ventricular chamber. (*F*) Lateral view at later stage in study indicates that the aorta occupies a normal position. Arrow points to one of the vessels arising from the aortic arch. The pulmonary trunk is partially obscured by the right and left atrial appendages. The area of increased density overlying the root of the aorta immediately beneath the letter "A" represents, in part, the left atrial appendage and, in part, the pulmonary trunk. The right atrial appendage which forms the anterior superior margin of the heart in this view obscures the anterior portion of the pulmonary trunk. Comparison with *D* indicates the manner in which the atrial appendages may, in part, obscure the pulmonary trunk and make it difficult to evaluate the anatomic relation of that vessel to the aorta.

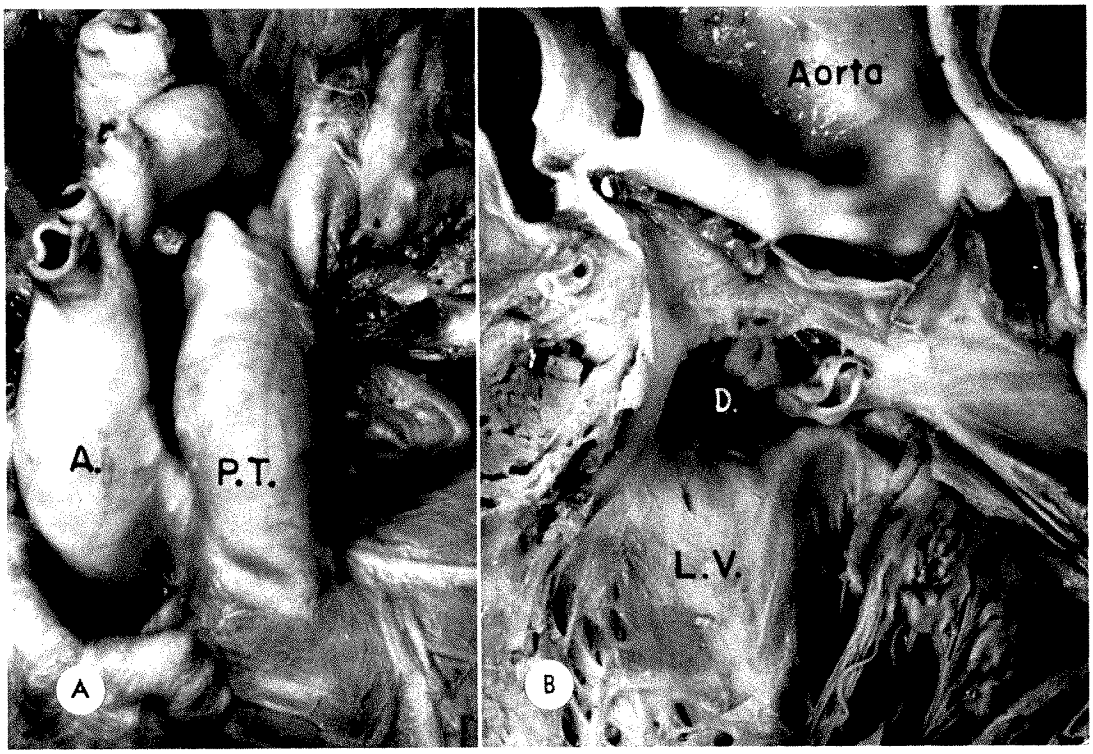

Fig. 4. (*A*) The great vessels viewed from in front. The aorta (A.) and the pulmonary trunk (P. T.) are normally interrelated. The two vessels are of about equal diameter. (*B*) Left ventricle (L. V.) and ascending aorta. Inferior to the aorta is the wide ventricular septal defect (D.). Accessory mitral valvular tissue presents into the posterior aspect of the ventricular septal defect.

protruded into the posterior aspect of the ventricular septal defect.

The view that pulmonary hypertension had been present was supported by 2 histologic facts: (1) the medium of the pulmonary trunk resembled that of the aorta, and (2) the intrapulmonary muscular arteries and arterioles exhibited excessive medial muscular tissue.

COMMENT

Demonstration of marked cardiomegaly with increased pulmonary vasculature in cases of tricuspid atresia without transposition of the great vessels is uncommon. Abrams and Alway[1] reviewed the literature on the roentgenographic features in 33 cases of tricuspid atresia. They stated that in most cases, the heart was either normal in size or only slightly enlarged. The pulmonary vascular markings were usually either slightly diminished or at the lower limits of normal. Astley and associates[2] reported on 9 cases of tricuspid atresia without transposition. They described the appearance of the pulmonary fields as "congested" in but 1 case; in another, pulmonary vasculature was described as "normal." Their remaining cases exhibited "oligemic" pulmonary fields. In the cases which exhibited "congested" lungs, there was a patent ductus arteriosus but no associated pulmonary stenosis.

In our experience, infants with tricuspid atresia who present with marked cardiomegaly and increased pulmonary vasculature have represented either one of 2 situations, each without pulmonary stenosis: (1) a moderately large ventricular septal defect and a normal or large right ventricular infundibular chamber without transposition, or (2) a common ventricle with transposed great vessels.[4] The manifestations in cases of the first of the 2 foregoing groups mimic those of tricuspid atresia with transposition of the great vessels, both clinically and on conventional roentgenograms. By angiocardiography those cases without transposition can readily be distinguished from those with transposition and a single ventricle.

SUMMARY

The pathologic findings are correlated with angiocardiographic observations in a case of tricuspid atresia without transposition of the great vessels or pulmonary stenosis.

Tricuspid atresia without pulmonary stenosis is usually associated with a single ventricle and transposed great vessels. The type of case reported here is uncommon. Distinction from the more common variety of tricuspid atresia without pulmonary stenosis may be made by angiocardiography.

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THE SPECTRUM OF CONGENITAL HEART DISEASE ASSOCIATED WITH CYANOSIS IN ADULTS*

ANGIOCARDIOGRAPHIC FINDINGS

By S. DAVID ROCKOFF, M.D., M.Sc. (Radiology),† *and* DEAN T. MASON, M.D.‡

BECAUSE of the hemodynamic burden caused by most types of congenital heart malformations associated with cyanosis and the complications due to secondary polycythemia, the occurrence of such defects is uncommon in adults. Moreover, if one excludes from these the patients who have reversed shunts due to pulmonary hypertension, congenital heart disease associated with cyanosis is rare in adults. Angiocardiography is relied upon for the definitive diagnosis in such cases. It is our purpose to present the spectrum of congenital heart disease associated with cyanosis which can occur in adults (Table I), stressing the unusual forms which may be seen, the angiocardiographic features of such cases, and the hemodynamic factors which affect longevity. Several of these patients are of even greater interest because of associated cardiovascular abnormalities which were demonstrated angiocardiographically.

REPORT OF CASES

VENTRICULAR SEPTAL DEFECT WITH PULMONARY HYPERTENSION (EISENMENGER'S COMPLEX) WITH CORONARY ARTERIOVENOUS FISTULA

Case I. H.G., N.I.H. No. 03-53-77. This 20 year old white mongoloid male was admitted with a history of cyanosis and a heart murmur since birth. In early childhood, squatting and syncopal episodes occurred with exertion. For several years prior to admission he had been limited by dyspnea and upper respiratory infections. On physical examination there was generalized cyanosis and clubbing. There was a right ventricular lift and a palpable pulmonic second sound. Auscultation at the base revealed a single second sound and a loud systolic ejection sound followed by a short grade II/VI midsystolic murmur. A faint continuous murmur was heard along the right and left sternal borders. The electrocardiogram revealed right ventricular hypertrophy and strain, right axis deviation, and right atrial enlargement. The chest roentgenograms showed an enlarged pulmonary artery and right ventricle and increased pulmonary vascularity. The systemic arterial oxygen saturation was 78.5 per cent and the hematocrit 73 per cent. At cardiac catheterization, the pulmonary arterial and right ventricular systolic pressures were 120 mm. Hg and were balanced with the systemic pressure. A large right-to-left shunt was indicated at the ventricular level by cardiogreen dye curves. The catheter passed through an interatrial communication. Left ventricular angiocardiography (Fig. 1, *A* and *B*) and subsequent retrograde aortography (Fig. 2) were performed. From these and the cardiac catheterization data, the diagnosis was established.

Comment: Eisenmenger's complex is a ventricular septal defect with a right-to-left shunt secondary to pulmonary hypertension.[13] Angiocardiograms showed the presence of a ventricular septal defect with a normal pulmonic valve in this case (Fig. 1, *A* and *B*). The diagnosis of Eisenmenger's complex was made in conjunction with the cardiac catheterization data which showed an elevated pulmonary artery pressure (120 mm. Hg) and desaturation of the systemic arterial blood (78.5 per cent O_2). Survival to adulthood of such patients has been reported with some frequency.[38] It is of interest that this patient presented with a continuous murmur in association with cyanosis, a combination which has been said to be almost pathognomonic of truncus arteriosus,[36] but in this instance was due to a coronary arteriovenous fistula (Fig. 2).

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TABLE I

CONGENITAL HEART DISEASE ASSOCIATED WITH CYANOSIS IN ADULTS*

Defect†	Case	Relative Survival into Adulthood
1. Patent ductus arteriosus with pulmonary hypertension		Frequent
2. Atrial septal defect with pulmonary hypertension		Frequent
3. Ventricular septal defect with pulmonary hypertension (Eisenmenger's complex)	I	Infrequent
4. Pulmonic stenosis with interatrial communication (Trilogy of Fallot)	II	Infrequent
5. Tetralogy of Fallot		Infrequent
6. Tetralogy of Fallot with atrial septal defect (Pentalogy of Fallot)	III	Infrequent
—Pentalogy of Fallot with corrected transposition of the great vessels	IV	Extremely rare
7. Ebstein's anomaly of the tricuspid valve	V	Infrequent
8. Tricuspid atresia	VI	Extremely rare
9. Single ventricle		Occurs only with associated pulmonic stenosis
10. Total anomalous pulmonary venous drainage	VII	Extremely rare
11. Pulmonary atresia with normal aortic root (Pseudotruncus)		Extremely rare
12. Truncus arteriosus	VIII	Extremely rare
13. Complete transposition of the great vessels		Occurs only with associated pulmonic stenosis[29]

*Modified from Keith, J. D., Rowe, R. D., and Vlad, P.[21]

† Cases with defects numbers 1 and 2 have not been presented because of their relatively common occurrence in adulthood. A case with defect number 5 is not shown because the angiographic characteristics are shown in the case illustrating defect number 6. Cases with defects numbers 9, 11 and 13 have not been presented because we have not performed angiocardiography on adults with these disorders.

TRILOGY OF FALLOT WITH MESOVERSION

CASE II. A.P., N.I.H. No. 02-75-25. This 29 year old white female was admitted with a history of a heart murmur and cyanosis since infancy. Physical examination revealed generalized cyanosis and clubbing. There was a right ventricular lift, a palpable systolic second sound and a systolic thrill at the base. Auscultation revealed a grade IV/VI systolic ejection murmur followed by a single second sound over the pulmonary outflow tract. Systemic arterial oxygen saturation was 80.5 per cent and the hematocrit was 56 per cent. Right heart catheterization revealed an atrial septal defect. The pulmonary artery was not entered. Dye curves revealed a large right-to-left shunt and a small left-to-right shunt at the atrial level. The right ventricular and systemic pressures were balanced. There was no evidence of a shunt at the ventricular level. Angiocardiography with injection into the left atrium (Fig. 3, *A* and *B*) and into the right atrium (Fig. 4) was performed and, in conjunction with the catheterization data, the diagnosis was made. At operation, mesoversion was confirmed and a normal pulmonic valve was noted, beneath which was a discrete ridge of fibromuscular tissue. This was resected and a teflon prosthesis was secured in the atrial septal defect. At the completion of the procedure, there was no significant residual pulmonic gradient. The postoperative course was uneventful and the patient has done well since surgery.

Comment. Trilogy of Fallot is an interatrial communication in combination with pulmonic stenosis.[20] This patient is unusual in that the pulmonic stenosis was infundibular rather than valvular.[33] Angiocardiographically, the diagnosis of trilogy of Fallot is made by the demonstration of an atrial septal defect and pulmonic stenosis, in the presence of an intact ventricular septum. In this patient the heart shows the rotational anomaly of incomplete dextroversion (mesoversion)[1] in which the longitudinal axis of the interventricular septum is along the midsagittal axis of the chest, the position of the ventricles in the postero-

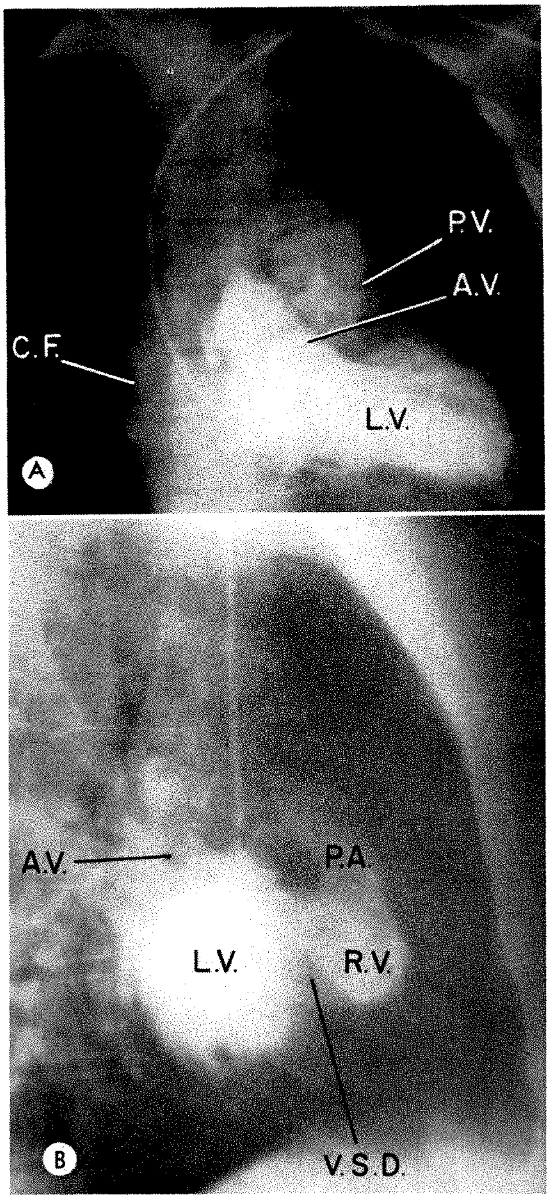

FIG. 1. Case I. Ventricular septal defect with pulmonary hypertension (Eisenmenger's complex) with coronary arteriovenous fistula. (*A* and *B*) Left ventricular (L.V.) angiocardiograms show a large ventricular septal defect (V.S.D.) with normally appearing pulmonic valve (P.V.) and a normal pulmonary outflow region (P.A.) of the right ventricle (R.V.). An abnormal channel opacifies from the right coronary artery (C.F.).

anterior view being similar to that of a normal left anterior oblique view. Also, the right atrium overlies the right ventricle in frontal projection and the pulmonary outflow tract is medially positioned. Similarly, the left atrium is superimposed on the left ventricle and, as seen in this patient, there is characteristically a left aortic arch. The position of the great vessels might cause mesoversion to be mistaken for corrected transposition of the great vessels (see Case IV). Right ventricular hypertension and decreased right ventricular compliance, secondary to the pulmonic outflow obstruction, lead to right atrial hypertension and shunting of blood from right-to-left through the interatrial communication. Survival to adulthood is infrequent.[10,18]

PENTALOGY OF FALLOT

CASE III. E.M., N.I.H. No. 02-40-17. This 39 year old white female was admitted with a history of a heart murmur, cyanosis and squatting during infancy and childhood. During early adult life, she was only moderately limited and at the age of 36 years successfully completed a pregnancy. Physical examination revealed moderate clubbing and cyanosis. There was a right ventricular lift, a decreased pulmonic closure sound, a systolic thrill and a grade IV/VI harsh systolic ejection murmur over the pulmonary outflow tract. The electrocardiogram revealed right axis deviation and right ventricular hyper-

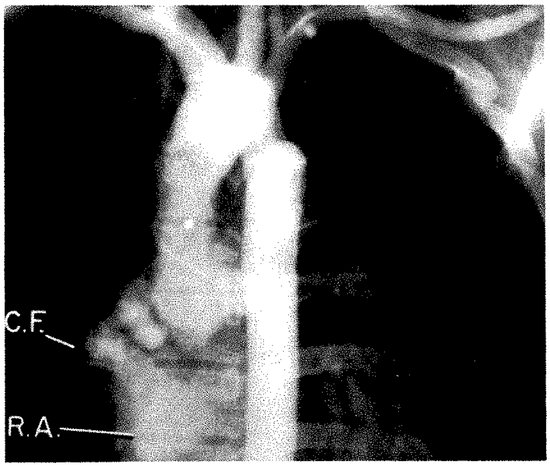

FIG. 2. Case I. Ventricular septal defect (Eisenmenger's complex) with coronary arteriovenous fistula. A retrograde aortogram shows the coronary arteriovenous fistula (C.F.) with contrast material shunting from the aorta to the right atrium (R.A.). Note incidental congenital deformity of descending portion of aortic arch.

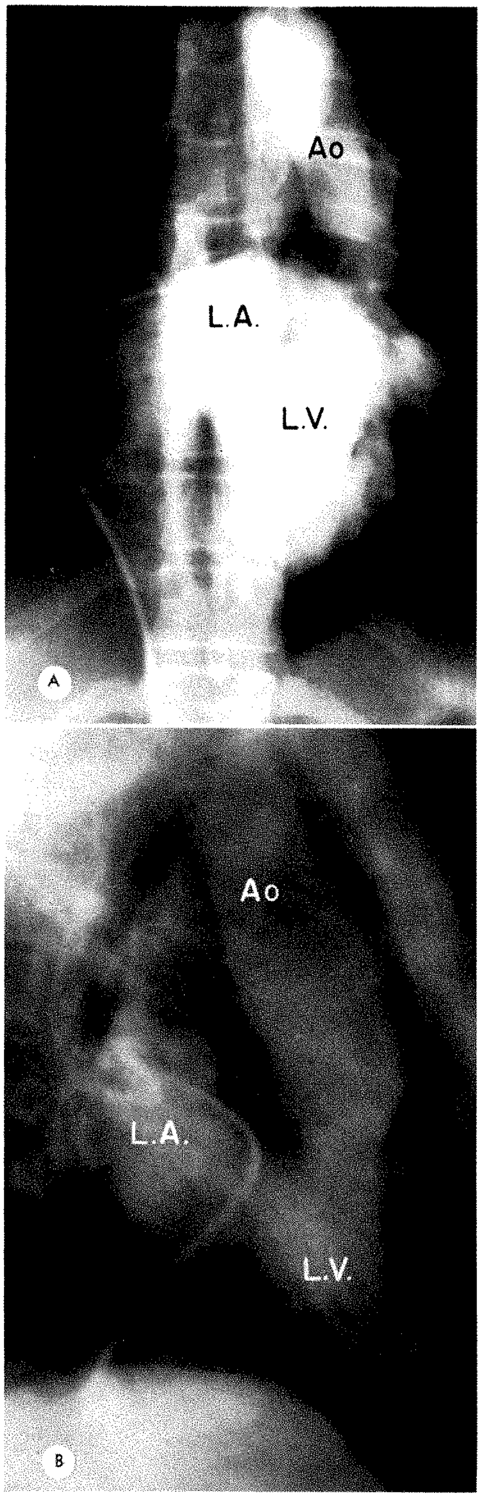

Fig. 3. Case ii. Trilogy of Fallot with mesoversion. (*A* and *B*) Injection of contrast material into the left atrium (L.A.) opacified the left ventricle (L.V.) and aorta (Ao). The aorta is unusual in that it ascends and descends on the left and, in lateral projection, is anteriorly placed. The left ventricle overlies the left atrium in frontal projection, is anteriorly placed in lateral projection, and the plane of the interventricular septum is along the mid-sagittal axis of the chest.

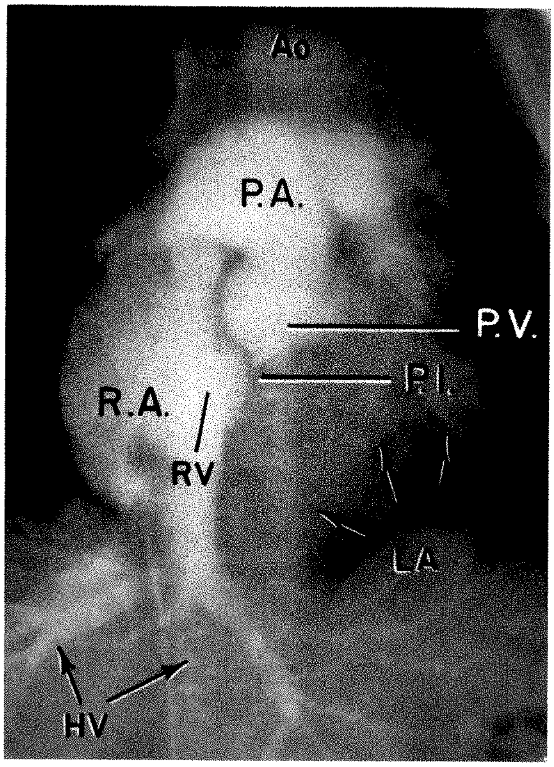

Fig. 4. Case ii. Trilogy of Fallot with mesoversion. With injection of contrast material into the right atrium (R.A.), opacification of a small right ventricle (RV) which overlies the right atrium is obtained. Pulmonic infundibular stenosis (P.I.) is identified. The pulmonic valvular leaflets (P.V.) are seen to be normal and the somewhat dilated pulmonary artery (P.A.) is central in position. There is faint opacification of the left atrium (LA) and aorta (Ao) due to the presence of the atrial septal defect. There is marked reflux of contrast material into the hepatic veins (HV).

trophy. The plain roentgenograms of the chest demonstrated concavity in the region of the main pulmonary artery and decreased pulmonary vascularity. The hematocrit was 58 per cent and the resting systemic arterial oxygen saturation 90.3 per cent. At right heart catheterization, an atrial septal defect and a ventricular septal defect were easily crossed. The pulmonary artery pressure was 15/4 mm. Hg and

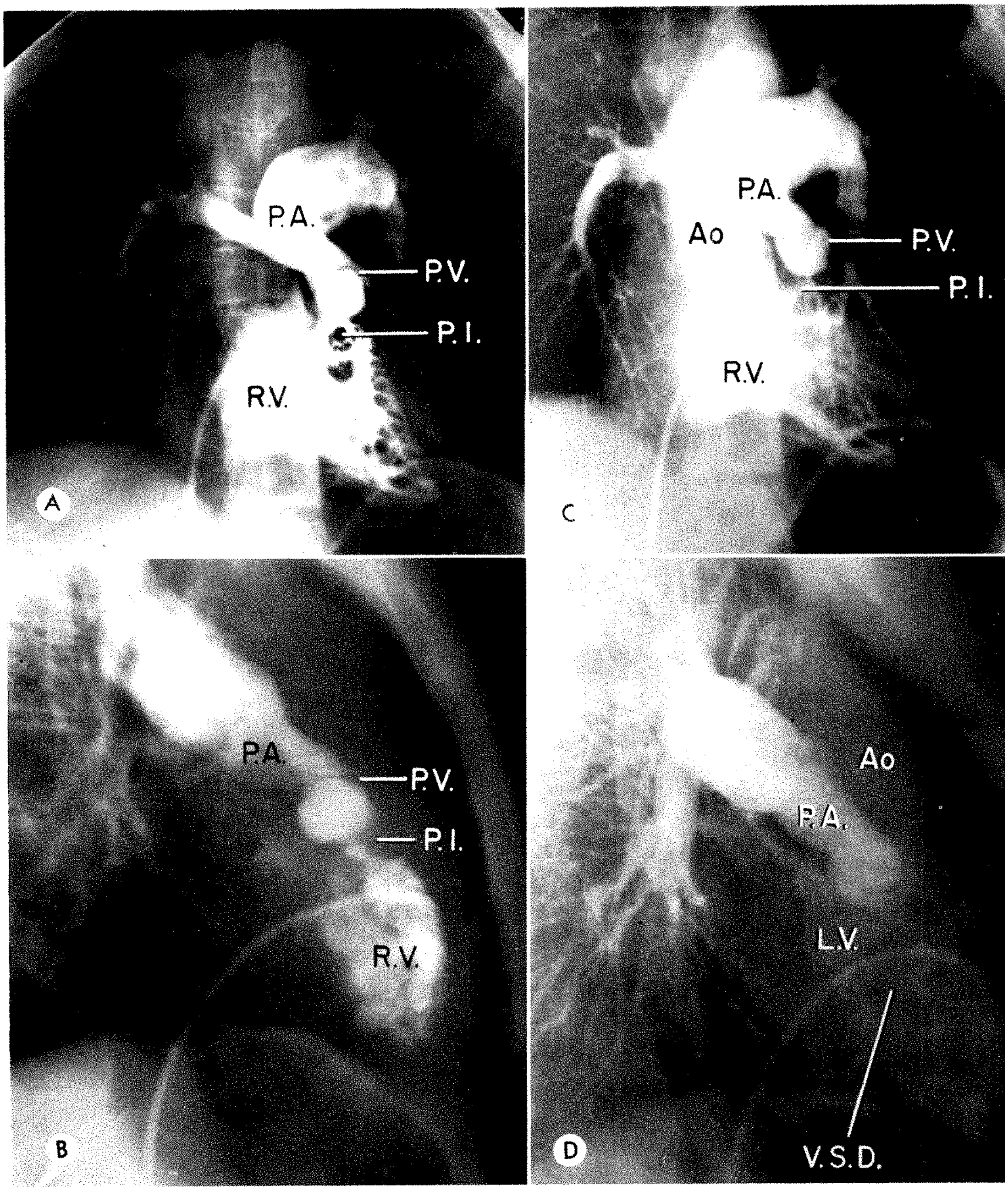

FIG. 5. Case III. Pentalogy of Fallot. (*A*, *B*, *C* and *D*) After injection of contrast material into the ri ventricle (R.V.), opacification of the pulmonary artery (P. A.) and aorta (Ao) and faint opacification the left ventricle (L.V.) and ventricular septal defect (V.S.D.) is noted. The thickened and domed pulmo valvular leaflets (P.V.) and the pulmonary infundibular narrowing (P.I.) are demonstrated. Poststeno dilatation of the left main pulmonary artery and the small caliber of the peripheral pulmonary ves are seen. In the lateral projection, some rotation of the great vessels is noted in that the aorta anterior to the pulmonary artery.

the right ventricular pressure, 110/0 mm. Hg. Cardiogreen dye curves revealed a moderate right-to-left and a small left-to-right shunt at the ventricular level and a small left-to-right shunt at the atrial level. The diagnosis was established on the basis of the catheterization data and the angiocardiographic findings (Fig. 5, *A–D*). Corrective surgery was contemplated, but the patient was found to be pregnant and the operation was delayed until after delivery.

Comment. A pentalogy of Fallot is an interatrial communication, in addition to the pulmonic stenosis, the right ventricular hypertrophy and the ventricular septal defect with over-riding of the aorta seen in tetralogy of Fallot.[22] Angiocardiographically, in the patient presented (Fig. 5, *A–D*) the diagnosis of a ventricular septal defect with overriding of the aorta and pulmonic valvular and infundibular stenosis was made, which is indicative of tetralogy of Fallot. The additional presence of the interatrial communication was established at cardiac catheterization. The cyanosis in pentalogy of Fallot is, as in tetralogy of Fallot, due to a right-to-left shunt through the ventricular septal defect. As in tetralogy, most cases become progressively more cyanotic and dyspneic after the first few months of life, and develop increasingly severe symptoms after puberty that terminate in death at about the end of the second decade. However, infrequent exceptions have been reported in which unoperated patients have survived into adulthood.[2,27,38]

PENTALOGY OF FALLOT WITH CORRECTED TRANSPOSITION OF THE GREAT VESSELS

CASE IV. A.C., N.I.H. No. 04-02-28. This 38 year old white female had a history of a heart murmur and cyanosis since birth. She was limited by moderately severe dyspnea on exertion and syncopal episodes and, as an adult, angina pectoris. On physical examination there was a diffuse ventricular lift over the precordium and a systolic thrill with a grade III/VI systolic murmur along the upper left sternal border. The liver was enlarged and tender and there was 3 plus bilateral ankle edema. The electrocardiogram revealed complete heart block, right axis deviation, right ventricular hypertrophy, and right atrial enlargement. The hematocrit was 62 per cent and the systemic arterial oxygen saturation 61.6 per cent. Right heart catheterization revealed an interatrial septal defect. Only the anterior ventricle could be entered. The pulmonary artery could not be entered. Cardiogreen dye curves from the left atrium, anterior ventricle, and superior vena cava all had a left sided appearance time, suggesting a large right-to-left shunt. The angiocardiographic findings are shown in Figure 6, *A*, *B* and *C*. At surgery, the patient had a left subclavian-pulmonary artery anastomosis established with a teflon graft. However, postoperatively the patient developed congestive failure, pulmonary infection and cardiac arrhythmias and expired. Postmortem examination confirmed the diagnosis.

Comment. A patient with corrected transposition of the great vessels and no other associated defects has a normal longevity.[9,31] This patient's cardiovascular illness was due to a pentalogy of Fallot with a hypoplastic systemic ventricle (Fig. 6, *A*, *B* and *C*). It is apparent from the angiographic studies that this patient was receiving virtually all of her systemic circulation from a large venous ventricle through a ventricular septal defect. Considering the severity of this patient's cardiovascular defects, it is most surprising that she lived to the age of 38 years.[3,31] The angiographic characteristics by which the associated corrected transposition of the great vessels is determined include positional transposition of the great vessels at their origins and anatomic connection of the pulmonary artery to the functional venous ventricle and of the aorta to the functional systemic ventricle, despite the positional transposition of the great vessels. Other characteristics include a trabeculated appearance of the systemic ventricle suggesting that it is anatomically a "right ventricle" (not well seen in this patient because of hypoplasia) and a smooth-walled appearance of the venous ventricle suggesting that it is anatomically a "left ventricle."

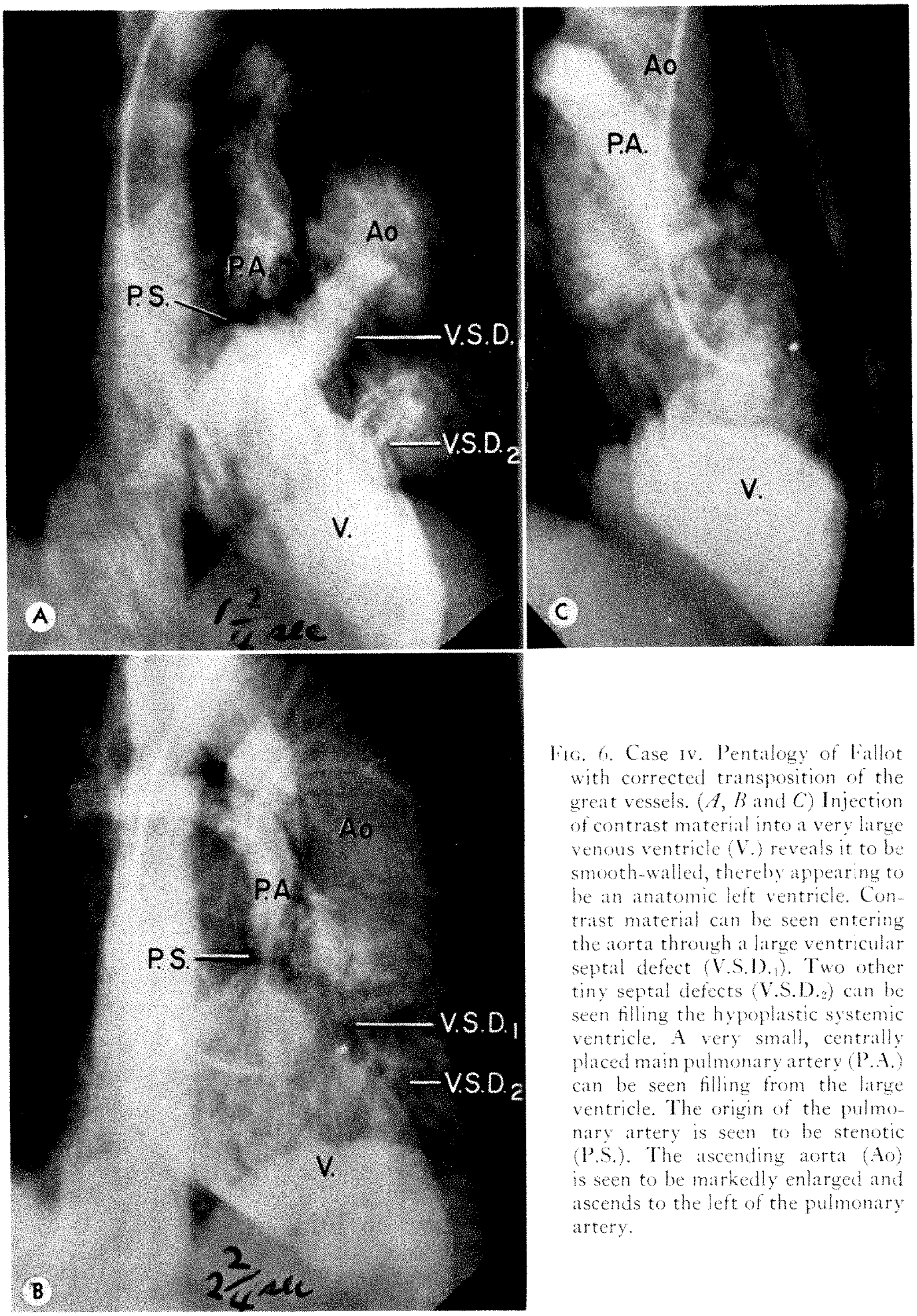

Fig. 6. Case iv. Pentalogy of Fallot with corrected transposition of the great vessels. (*A*, *B* and *C*) Injection of contrast material into a very large venous ventricle (V.) reveals it to be smooth-walled, thereby appearing to be an anatomic left ventricle. Contrast material can be seen entering the aorta through a large ventricular septal defect (V.S.D.$_1$). Two other tiny septal defects (V.S.D.$_2$) can be seen filling the hypoplastic systemic ventricle. A very small, centrally placed main pulmonary artery (P.A.) can be seen filling from the large ventricle. The origin of the pulmonary artery is seen to be stenotic (P.S.). The ascending aorta (Ao) is seen to be markedly enlarged and ascends to the left of the pulmonary artery.

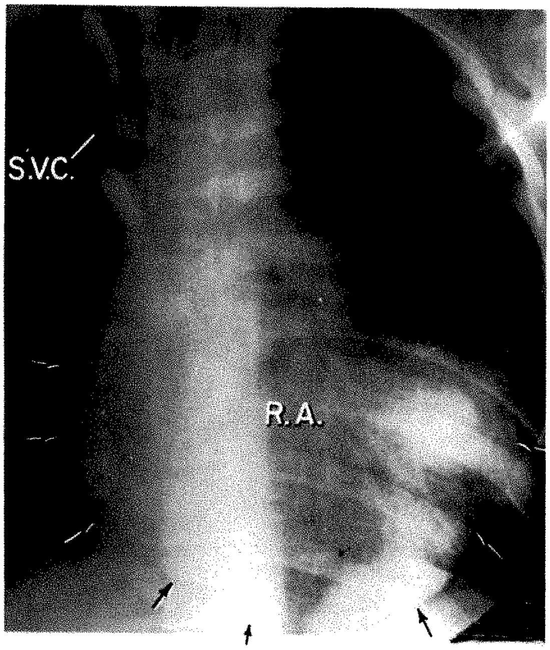

Fig. 7. Case v. Ebstein's anomaly. An intravenous angiocardiogram reveals a markedly enlarged right heart (arrows), most of which represents right atrium (R.A.), the exact limits of which cannot be defined on this study.

EBSTEIN'S ANOMALY OF THE TRICUSPID VALVE

Case v. J.C., N.I.H. No. 00-28-14. This 20 year old white male was admitted with a history of intermittent cyanosis, dyspnea and syncopal episodes since birth. Physical examination revealed generalized cyanosis and clubbing, a protodiastolic gallop and a grade II/VI precordial systolic murmur. The electrocardiogram revealed right bundle branch block, right axis deviation, and right atrial hypertrophy. Plain roentgenograms of the chest showed generalized cardiac enlargement and decreased pulmonary vascularity. The hematocrit was 80 per cent and the arterial oxygen saturation 73.7 per cent. Cardiac catheterization revealed normal right atrial and ventricular pressures and the presence of an interatrial communication. Figure 7 is the intravenous angiocardiogram from which, in conjunction with the cardiac catheterization data, the diagnosis of Ebstein's anomaly of the tricuspid valve was postulated. At surgery, the atrial septal defect was closed but the patient expired in the postoperative period. A postmortem examination revealed an atrial septal defect and Ebstein's anomaly of the tricuspid valve with downward displacement of the posterior line of attachment of greatly enlarged valve leaflets.

Comment. Ebstein's anomaly of the tricuspid valve is a malformation of the right atrioventricular ostium in which there is downward displacement of the tricuspid valve toward the cardiac apex and usually deformation of the valvular leaflets. Acyanotic cases are extremely rare and all of the cyanotic ones have had atrial septal defects demonstrated.[16] Angiocardiographically, a very large right atrium is seen (Fig. 7) which, because of its size, is frequently difficult to opacify well. It is also frequently possible to visualize a relatively small right ventricle,[37] but a common problem is the determination of where the enlarged atrium ends and the diminutive ventricle begins. The cyanosis is due to a right-to-left shunt through the atrial septal defect secondary to an elevated pressure in the right atrium. In the majority of the cases, the cyanosis appears at birth, early infancy or insidiously between the ages of 3 and 12. Survival to adulthood in Ebstein's anomaly is relatively infrequent.[16,32,37]

TRICUSPID ATRESIA

Case vi. A.H., N.I.H. No. 03-87-02. This 27 year old Mexican male was admitted with a history of progressive cyanosis, exertional dyspnea and a heart murmur since infancy. At the age of 17, at another hospital, he underwent a left subclavian-pulmonary artery anastomosis after a diagnosis of tetralogy of Fallot had been made. However, his cyanosis improved only transiently. Physical examination revealed severe cyanosis and clubbing. There was a left ventricular thrust, a grade II/VI systolic ejection murmur and a faint continuous murmur at the base. The electrocardiogram revealed left ventricular hypertrophy, left axis deviation, and left atrial hypertrophy. The systemic arterial oxygen saturation was 88.5 per cent and the hematocrit 82 per cent. At right heart catheterization, the catheter crossed an interatrial communication and then entered a ventricular chamber where a systemic pressure was recorded. The right ventricle and the pulmonary artery could not be entered. Cardio-

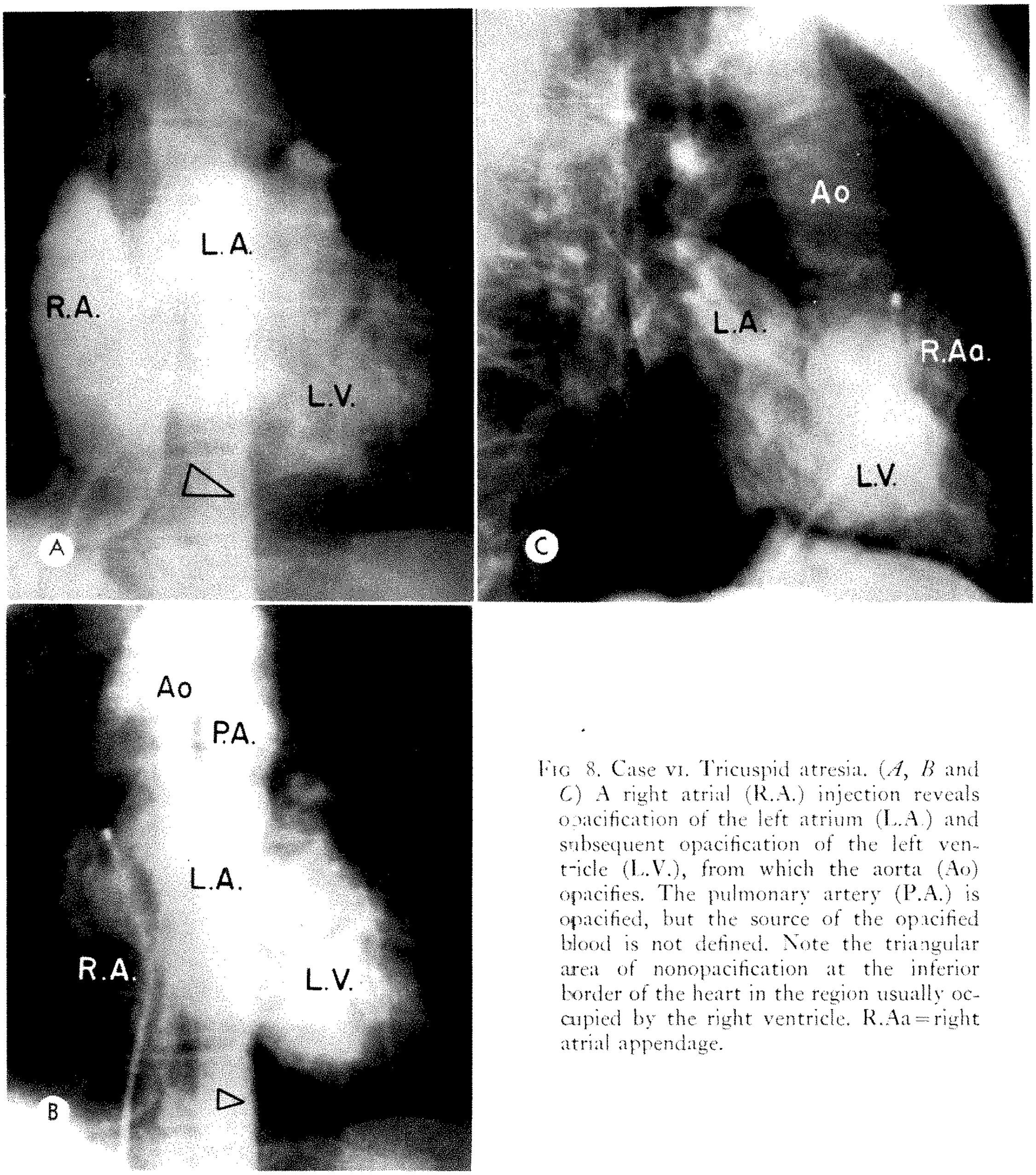

FIG 8. Case VI. Tricuspid atresia. (*A*, *B* and *C*) A right atrial (R.A.) injection reveals opacification of the left atrium (L.A.) and subsequent opacification of the left ventricle (L.V.), from which the aorta (Ao) opacifies. The pulmonary artery (P.A.) is opacified, but the source of the opacified blood is not defined. Note the triangular area of nonopacification at the inferior border of the heart in the region usually occupied by the right ventricle. R.Aa = right atrial appendage.

green dye curves from the right and left sides of the heart all had a left-sided appearance time, indicating a right-to-left shunt at the atrial level. From the cardiac catheterization and angiocardiograms (Fig. 8, *A*, *B* and *C*), the diagnosis of tricuspid atresia was made. The patient underwent cardiac surgery at which time an anastomosis was created between the distal end of the divided right pulmonary artery and the side of the superior vena cava. The superior vena cava was then ligated proximal to this anastomosis in order to create a channel to the pulmonary arteries for oxygenation of venous blood. At the conclusion of the procedure, the patient's cyanosis was markedly decreased. Postoperatively, however, considerable bleeding occurred into the pleural cavity, the patient developed cardiac arrest and expired. Postmortem examination revealed tricuspid atresia, a large atrial septal defect, an anatomically closed ventricular septal defect of the muscular portion, a hypoplastic right ventricle and pulmonary trunk, a probe patent left subclavian-pulmonary artery anastomosis and a highly developed bronchial artery circulation.[28]

Comment. The survival into adulthood of a patient with tricuspid atresia is extremely uncommon.[12] A recent survey of the literature by us revealed only 5 patients who lived longer than the patient reported herein (27 years).[7,14,17,19] Only 1 was pathologically proven,[7] and none had angiocardiographic studies. The angiocardiographic features by which the diagnosis of tricuspid atresia can be made are shown in Figure 8, *A*, *B* and *C*. These include dense opacification of the left atrium and left ventricle after a right atrial injection of contrast material, with little or no opacification of the right ventricle. The finding of an unopacified triangular area in the region usually occupied by the right ventricle is fairly characteristic of tricuspid atresia and is well seen in this case. The source of the opacification of the pulmonary artery seen in Figure 8*B* is not clearly identified in this study. Longevity in tricuspid atresia is related to an optimal pulmonary blood flow which, in turn, is regulated by the development of the pulmonary trunk and right ventricle, the size of the ventricular septal defect, and the extent of collateral bronchial circulation. Because this patient's cyanosis returned shortly after his subclavian-pulmonary artery anastomosis, it is assumed that this operation probably did not significantly affect his longevity. This patient's progressive increase in cyanosis probably was caused by the gradual spontaneous closure of the ventricular septal defect.[28]

TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE

Case vii. H.M., N.I.H. No. 03-80-03. This 33 year old white male was admitted with a history of mild cyanosis and a heart murmur since early childhood. Except for mild exertional dyspnea and fatigue, he was asymptomatic. On physical examination there was mild cyanosis without clubbing. There was a marked right ventricular lift and a palpable second sound at the base which was split and fixed with respiration. At the left sternal border, the opening snap of the tricuspid valve and a late diastolic atrial sound were heard. An early systolic ejection murmur was heard over the pulmonary outflow tract and a continuous murmur was heard over the right clavicle. The electrocardiogram revealed right ventricular hypertrophy, right axis deviation, right bundle branch block, and left atrial hypertrophy. The hematocrit was 47 per cent and the resting arterial oxygen saturation was 89.1 per cent. At right heart catheterization the pulmonary artery pressure was found to be 60/22 with no gradient across the pulmonic valve. An interatrial communication was easily crossed. Cardiogreen dye curves indicated a large right-to-left shunt and a large left-to-right shunt at the atrial level. On the basis of the cardiac catheterization and the angiocardiographic findings (Fig. 9, *A* and *B*), the diagnosis was made. Corrective surgery was performed by connecting the anomalous pulmonary venous trunk to the left atrium and by closing the atrial septal defect with a teflon patch. The patient was discharged without cyanosis 4 weeks postoperatively.

Comment. Total anomalous pulmonary venous drainage is an anomaly in which all of the pulmonary venous blood drains into the right side of the heart. The great majority of patients with this abnormality die in infancy or early childhood.[8,23] However, in rare cases as with this patient, survival into adulthood has occurred if the atrial septal defect is large and the pulmonary vascular resistance is not too elevated.[4,15,26,35] Cyanosis occurs because mixed arterial and venous blood is shunted from the right atrium through an interatrial communication into the systemic circulation. Angiocardiographically, opacification of pulmonary veins which ultimately drain into the right atrium, after injection of contrast material into the pulmonary arteries, is diagnostic of this entity. The anomalous pulmonary veins may drain into the right atrium by way of the superior vena cava, as in this case (Fig. 9, *A* and *B*), directly into the right side of the heart[30] or even into veins below the diaphragm, although the patients in whom the drainage is into the portal vein die in infancy.[24,25] The angiographic appearance of drainage into the right superior vena cava by way of a persistent left superior vena cava is shown in this case. This configuration on plain roentgenograms is characteristic of this entity and is frequently referred to as "the snowman."

TRUE TRUNCUS ARTERIOSUS (TYPE IV)

Case viii. A.J., N.I.H. No. 02-32-42. This 42 year old Hawaiian female was admitted with the history of cyanosis, heart murmur and squatting since childhood. One year prior to admission she developed dyspnea on exertion, ankle edema, and frequent upper respiratory infections. Physical examination revealed marked cyanosis and clubbing. There was a right ventricular lift, a single loud second sound, a continuous murmur at the base, and a grade II/VI systolic ejection murmur along the left sternal border. The liver was enlarged and there was 2 plus ankle edema. The electrocardiogram revealed right axis deviation, right ventricular hypertrophy, and right atrial enlargement. The plain roentgenograms of the chest demonstrated decreased pulmonary vascularity, a concavity in the region of the pulmonary artery, and a prominent aorta. Systemic arterial oxygen saturation was 55.2 per cent and the hematocrit was 68 per cent. At right heart catheterization, the right ventricular pressure was 140/5 mm. of Hg and the aortic pressure was 140/80 mm. of Hg. Cardiogreen dye curves sampled from the femoral artery and injected into the right ventricle and ascending aorta revealed a left-sided appearance time with evidence of markedly diminished pulmonary blood flow originating from the aorta. The cardiac catheterization findings, in conjunction with the angiocardiographic findings (Fig. 10, *A–D*) established the diagnosis. Palliative surgery was not felt indicated for this lesion.

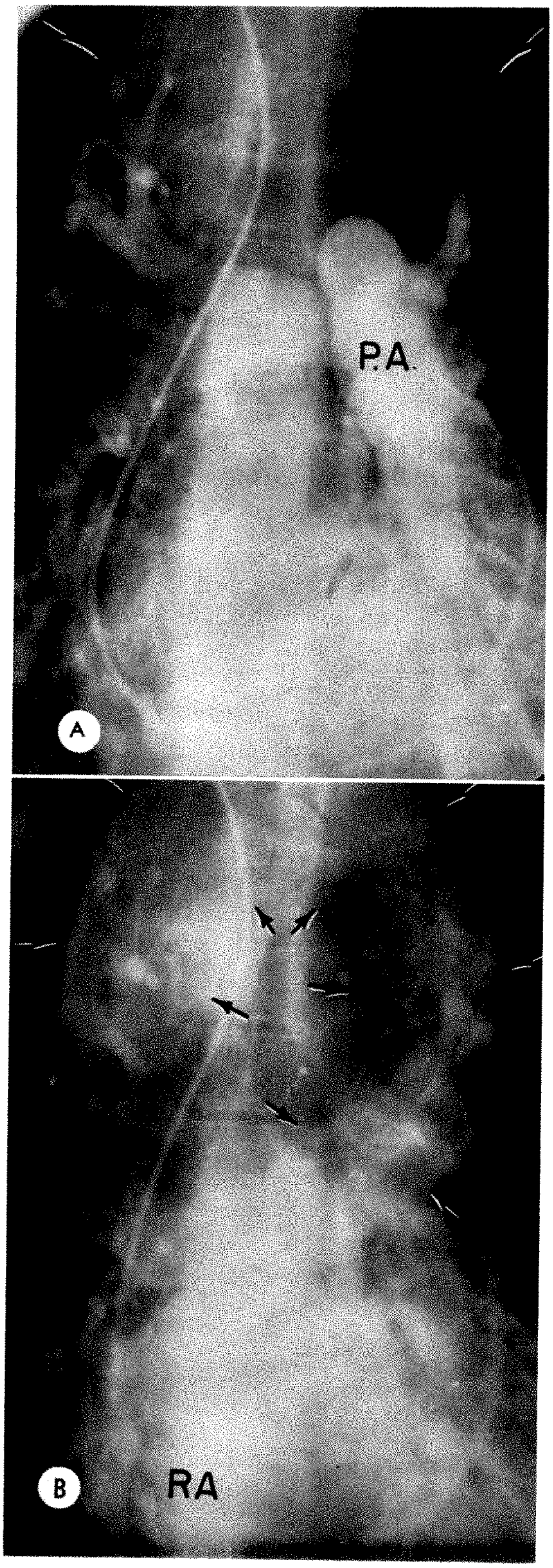

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Fig. 9. Case vii. Total anomalous pulmonary venous drainage. (*A* and *B*) With injection of contrast material into the pulmonary artery (P.A.), opacification of a large anomalous central pulmonary vein is seen, which opacifies the right atrium (R.A.) by way of a persistent left and right superior vena cava (arrows).

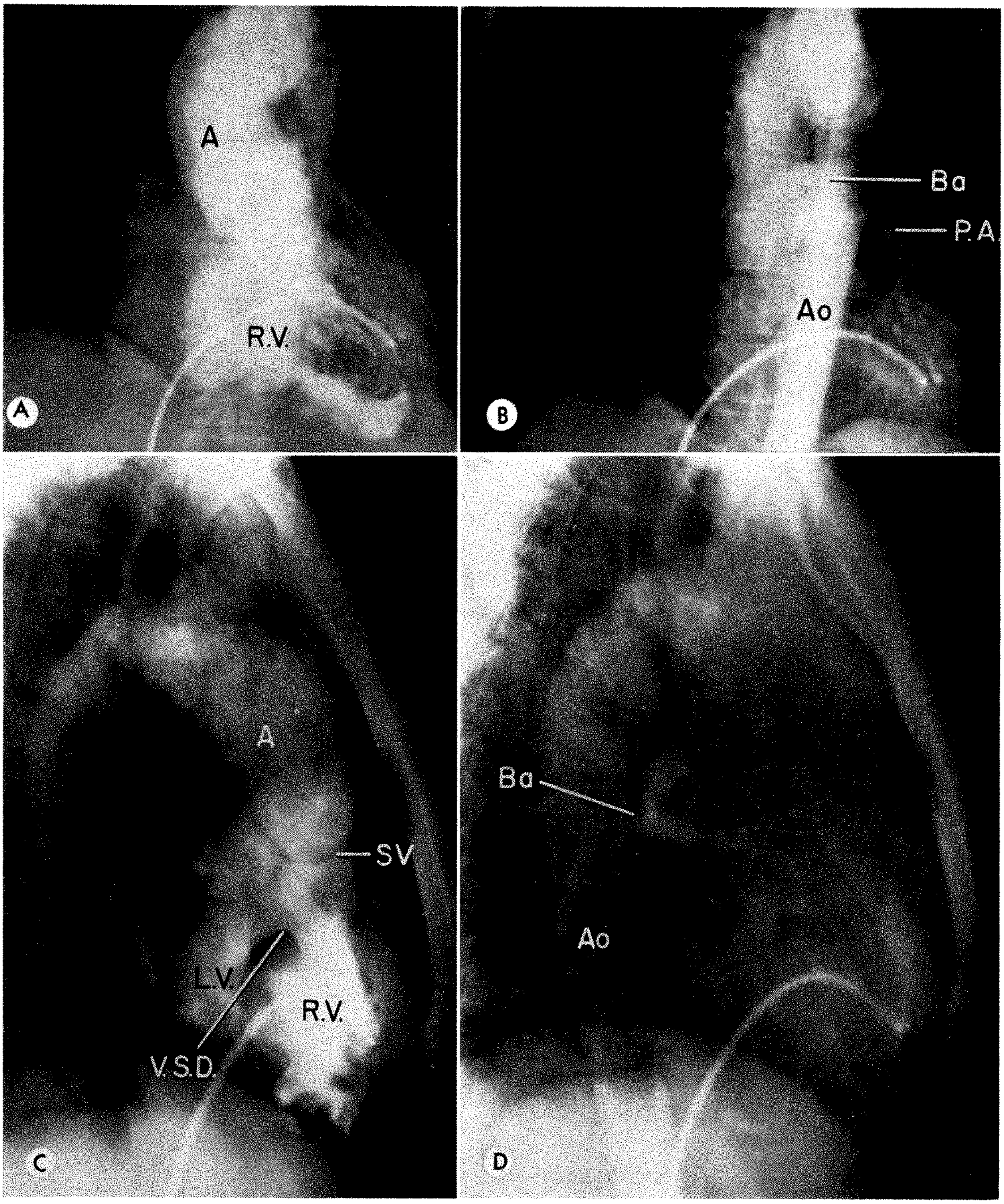

Fig. 10. Case viii. True truncus arteriosus. Type iv. (*A*, *B*, *C* and *D*) With the catheter in the right ventricle (R.V.), filling of the left ventricle (L.V.) through a large ventricular septal defect (V.S.D.) is seen. Overriding the septal defect is a single very large arterial trunk (A) and no evidence of a pulmonary artery remnant. The semilunar valvular leaflets (SV) are well seen and are normal. Bronchial arteries (Ba), arising from the descending aorta (Ao), can be seen filling pulmonary arteries (P.A.) in the left lower lung field.

Comment. Type IV persistent truncus arteriosus is characterized by a single arterial vessel arising from the heart with absent pulmonary arteries and ductus arteriosus, and with the arterial circulation to the lungs derived from the bronchial arteries. All of these characteristics are demonstrated angiocardiographically in Figure 10, *A–D*. The types of true truncus arteriosus other than demonstrated with this case are determined by the origin of the pulmonary blood supply.[6] The advanced age of this patient is unique for this entity.[5,11,34,40] The reason that this patient survived to the age of 42 years is not entirely explained, but apparently the bronchial circulation was adequate to sustain life. The reason for the cyanosis in this condition is obvious since, as can be seen in the angiocardiograms, the systemic circulation is derived to a great extent from the right ventricle.

SUMMARY

Congenital heart disorders, especially those associated with cyanosis, are usually thought of as childhood diseases. However, in some instances, individuals with severe cyanotic defects have survived into adult life. In order to make the definitive diagnosis in such disorders, angiocardiography is essential. The angiographic and hemodynamic findings and factors influencing longevity are presented and discussed in 8 cyanotic adult patients. Such defects, therefore, should be considered in the differential diagnosis of congenital heart disease in the cyanotic adult, along with the more common malformations.

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ROENTGEN FEATURES OF DEXTROROTATION OF THE HEART*

REPORT ON 49 CASES

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MALPOSITION of the heart into the right hemithorax is of considerable importance to the radiologist because he is often the first to encounter the abnormality. Of course, he must first determine whether the malposition is real and not apparent owing to poor positioning or scoliosis of the spine. Indeed, the conventional roentgenogram of the chest may be very revealing and readily demonstrate mirror-image dextrocardia.[13,14] This is classic dextrocardia and is almost always associated with complete situs inversus and is rarely complicated by associated cardiovascular anomalies. In contrast, dextrorotation or dextroversion of the heart is a different entity, morphologically and embryologically and is not associated with situs inversus,[3,14] but is frequently complicated by other cardiac malformations. Whereas the uncomplicated case of dextrorotation may be easy to detect, the majorty require additional studies such as: electrocardiography, especially vector electrocardiographic analysis, angiocardiography, and cardiac catheterization for definitive diagnosis. The radiologist, therefore, is not only in a position to recommend such special studies, but he can often determine whether dextroposition of the heart is caused by adjacent disease of the pulmonary parenchyma, pleura, or mediastinal structures.

MATERIAL AND METHODS

The data in this paper were compiled from a study of several thousand angiocardiographies performed in this center during the years 1948 to 1962 (Table 1). Serial angiocardiography, usually via intravenous injection (Robb-Steinberg method[18]), was performed in 45 patients. In 3 instances (Cases 3, 9 and 26) conventional roentgenography and electrocardiography were sufficiently characteristic to establish the diagnosis of dextrorotation of the heart without the need of angiocardiography. In another patient (Case 23) with anomalous pulmonary venous drainage, angiocardiography was not performed because exploratory operation was preferred.[24]

Usually two injections of contrast material were made for frontal and lateral studies; in a few cases, a single injection for biplane study sufficed. In some patients, selective angiocardiography was also performed to better define valvular deformities and shunts. For the same reasons, many of the patients had cardiac catheterization for detailed hemodynamic studies. Every patient had a complete history, physical examination, including multiple lead electrocardiographic and vector electrocardiographic determinations, routine blood and urine examinations, and conventional roentgenography of the chest in multiple views. Many patients had bronchography, especially of the right bronchial tree. One patient with an elevated diaphragm had artificial pneumoperitoneum in order to better outline the structure (Case 24).[24]

RESULTS

Dextrorotation of the heart was classified into two groups, depending on whether there were associated extracardiac or cardiovascular anomalies (Table 1). The sex

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incidence was almost equal, 26 males and 23 females. The ages varied from 3½ weeks to 69 years. Eight patients were Negro, the remainder were Caucasian. Among the extracardiac lesions were pectus excavatum, absence of the sternum, absence of the pleural reflections, bronchial malformation (especially of the right lung), partial absence of lobes of the right lung, bronchiectasis, and eventration of the diaphragm.

The associated cardiovascular anomalies, chiefly involving the great vessels, also fell into well-defined groups: congenital absence of the right pulmonary artery, hypoplasia of the right pulmonary artery, agenesis of the segmental blood supply of the right lung, partial absence of segments or lobes of the right lung, anomalous pulmonary venous drainage of the right lung into the inferior vena cava, aberrant arteries from the abdominal aorta connecting with the right lower lobe, and corrected transposition of the great vessels (Table 1). Coarctation and pseudocoarctation of the aorta were encountered (Cases 24[26] and 37[27]). The intracardiac shunts were atrial, ventricular and atrioventricular (ostium primum). A patent ductus arteriosus and ventricular septal defect were present in 1 patient (Case 35). Cases 47, 48, and 49 were unique in that, in addition to dextrorotation, there were dextrocardia and corrected transposition. A similar case of dextrorotation, dextrocardia, and corrected transposition in which there was a successful repair of an atrial septal defect and pulmonary stenosis was recently reported in the literature.[16]

Normally, on frontal roentgenograms, the right atrium forms the right border of the cardiac shilhouette, the right ventricle occupies three-fifths of the diaphragm, and the left ventricle lies over the remaining two-fifths of the diaphragm and forms the left border of the cardiac contour.[8] In dextrorotation unaccompanied by associated cardiovascular malformations, the longitudinal plane of the heart forms an angle of 30° to 45° with the sagittal plane of the thorax in the transverse plane of the body. This may be simulated by turning a patient with a normally placed heart into the left anterior oblique position. The displacement may also be produced by fixing the great vessels and swinging the heart to the right in the frontal plane (in pendulum fashion). As a result of such rotation, the two ventricles are seen to lie side by side; the right ventricle instead of being the anterior ventricle has actually become the "right" ventricle and the left ventricle is now the "left" ventricle instead of the posterior ventricle. The position of the atria is almost normal; the right atrium is posterior to the right ventricle, the superior vena cava is more medial and the left atrium is slightly anterior to the right atrium. The great vessels arise normally but the rotation to the right opens the loop between the ascending and descending aorta, while the main pulmonary artery is displaced medially (Fig. 1, *A–E;* and 2, *A–F*).[3] (*See page 346 for Fig. 1, B–E.*)

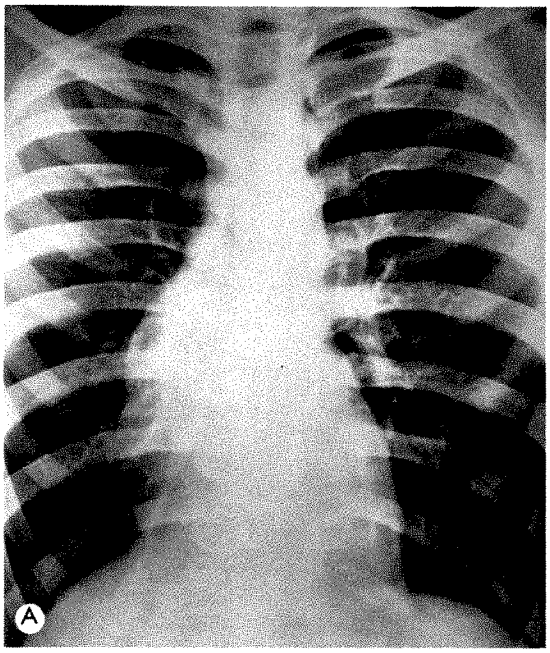


FIG. 1. Case 1. *Dextrorotation of the heart without associated cardiovascular anomalies.* (*A*) Conventional teleroentgenogram showing prominence of the right upper cardiac silhouette which was mistaken for a mediastinal tumor.

TABLE I

ANGIOCARDIOGRAPHIC FINDINGS IN DEXTROROTATION OF THE HEART

Case No.	Age (yr.)	Sex	Associated Anomalies and Disease	Findings	Remarks
(A) Extracardiac Anomalies					
1	19	M	None	Classic features of uncomplicated dextrorotation (Fig. 1, *B*, *C*, *D* and *E*)	Classic features of dextrorotation the heart in a patient without ot anomalies; referred because ri mediastinal tumor was suspec after routine roentgenogram (F 1*A*)
2	41	F	Pectus excavatum	Uncomplicated dextrorotation	Systolic murmur and abnor heart position led to studies; card catheterization normal
3	21	M	None	Not done because conventional chest roentgenogram and electrocardiogram showed classic dextrorotation	Referred because of unusual card position
4	10	F	Congenital absence of manubrium	Classic uncomplicated dextrorotation	Roentgenoscopy showed unusua pulsatile descending aorta (p viously published[3])
5	4	F	Absent right upper lobe (Fig. 2*B*); agammaglobulinemia	Classic uncomplicated dextrorotation (Fig. 2, *C*, *D*, *E* and *F*)	Bronchogram showed absence right upper lobe (Fig. 2*B*)
6	15	F	None	Minor degree of dextrorotation (Fig. 3, *A* and *B*), sometimes referred to as mesorotation	Referred because of systolic card murmur and prominent pulsa pulmonary artery
7	50	F	None	Classic uncomplicated dextrorotation	Referred because of dextroposit of heart
8	47	M	Eventration of left diaphragm	Dextrorotation of heart and great vessels	Roentgenogram previously p lished[8]
9	45	M	Eventration of left diaphragm	Not done	Classic findings on conventio roentgenogram and electrocard gram made angiocardiography necessary
10	50	F	Acquired rheumatic heart disease with mitral stenosis and left pleural effusion (Fig. 4*A*)	Dextrorotated right ventricle and pulmonary artery (Fig. 4*B*) with large dextrorotated left atrium and ventricle (Fig. 4*C*)	Closed heart operation (valvu plasty) followed by improveme cardiac chambers still dextrorota after aspiration of left pleural fl (Fig. 4*D*)
(B) Cardiovascular Anomalies					
11	3½	M	Absent right pulmonary artery; malformation (bud-like) of terminal bronchi of right lung	Absent right pulmonary artery with dextrorotation of heart (Fig. 5*B*)	Referred because of recurrent pn monia of right lung; mediasti herniation (Fig. 5*A*) mistaken atelectatic right upper lobe
12	22	F	Absent right pulmonary artery; right pulmonary artery arising from descending aorta; and malformed bronchi of right lung with bronchiectasis (Fig. 6, *B* and *C*)	Hypoplastic right pulmonary artery (Fig. 6*D*); systemic right pulmonary artery from descending aorta (Fig. 6*E*)	Developed asthmatic attacks; p monary function studies show bronchiolar obstruction; card catheterization disclosed mild pulmonary hypertension (33 mm. Hg) after exercise
13	14	F	Hypoplastic right pulmonary artery; systemic arteries from abdominal aorta into right lower lobe	Classic dextrorotation of heart; hypoplastic right pulmonary artery (Fig. 7, *B* and *C*); anomalous arteries from abdominal aorta into right lower lobe (Fig. 7*D*)	Ligation of anomalous arteries fr aorta resulted in disappearance dyspnea (previously published[23])
14	48	F	Hypoplastic right pulmonary artery	Uncomplicated dextrorotation with hypoplastic right pulmonary artery	Referred because of meager ri upper lobe vasculature and rig sided cardiac position

Table I (*Continued*)

Case No.	Age (yr.)	Sex	Associated Anomalies and Disease	Findings	Remarks
15	30	M	Hypoplastic right pulmonary artery	Hypoplastic right pulmonary artery and dextrorotation	Referred because of "dextrocardia"
16	19	M	Absent right upper lobe; malformed bronchi of right lung; hypoplastic right pulmonary artery; bronchial asthma	Dextrorotation of heart and great vessels	Prominent pulmonary artery found to be due to dextrorotation; wheezing caused by bronchospasm
17	9	F	Anomalous drainage of right pulmonary veins into inferior vena cava; persistent left superior vena cava; hypoplastic right pulmonary artery	Dextrorotation of heart; hypoplastic right pulmonary artery and left superior vena cava (Fig. 8*B*); anomalous drainage of right pulmonary veins into inferior vena cava (Fig. 8*C*)	Conventional roentgenogram (Fig. 8*A*) showed classic features of dextrorotation of heart and anomalous pulmonary veins of right lower lung
18	7	M	Anomalous drainage of pulmonary veins of right lung into inferior vena cava; hypoplastic right pulmonary artery; systemic arteries from aorta into right lower lobe; malformed right bronchi (Fig. 9*A*)	Dextrorotation of heart; hypoplastic right pulmonary artery (Fig. 9*B*); anomalous drainage of right pulmonary veins into inferior vena cava and abdominal aortic branches to right lower lobe (Fig. 9, *C* and *D*)	Chief complaints were recurrent infections of right lung
19	27	M	Anomalous drainage of right pulmonary veins into inferior vena cava and hypoplastic right pulmonary artery	Dextrorotation; hypoplasia of right pulmonary artery; anomalous drainage of right pulmonary veins into inferior vena cava	Asymptomatic; studied because of unusual conventional roentgenogram of chest (previously published[7])
20	41	M	Anomalous pulmonary venous drainage of right pulmonary veins into inferior vena cava; hypoplasia of right pulmonary artery	Dextrorotation; hypoplasia of right pulmonary artery; anomalous drainage of right pulmonary veins into inferior vena cava	Unusual roentgenogram of chest and roentgenoscopy suggested anomalous pulmonary venous drainage (previously published[7])
21	23	M	Anomalous drainage of right pulmonary veins into inferior vena cava; hypoplastic right pulmonary artery; distorted right pulmonary arterial segments	Dextrorotation; hypoplasia of right pulmonary artery with distorted segmental blood supply	Asymptomatic; abnormal routine conventional roentgenogram suggested anomalous pulmonary venous drainage (previously published[24])
22	23	F	Anomalous pulmonary venous drainage of right lung into inferior vena cava; hypoplastic right pulmonary artery	Anomalous pulmonary venous drainage of right lung into inferior vena cava; dextrorotation	Asymptomatic; abnormal right lung vasculature and cardiac rotation led to request for angiocardiographic study (previously published[24])
23	59	F	Anomalous pulmonary venous drainage into inferior vena cava; hypoplastic right pulmonary artery; eventration of right diaphragm; pleuropericardial adhesions	Angiocardiography recommended but exploratory operation of right thorax done because of "mass" in right chest	Operation established presence of anomalous pulmonary venous drainage of right lung into inferior vena cava, eventration of diaphragm, and pleuropericardial adhesions (previously published[24])
24	10	F	Anomalous right pulmonary venous drainage into inferior vena cava; hypoplasia of right pulmonary artery; eventration of right diaphragm; diaphragmatic and pericardial adhesions; coarctation of aorta	Dextrorotation of heart; anomalous right pulmonary venous drainage into inferior vena cava; hypoplasia of right pulmonary artery; coarctation of aorta	Pneumoperitoneum established diagnosis of eventration of right diaphragm; exploratory operation of right hemithorax corroborated angiocardiographic findings; coarctation was not repaired (previously published[26])
25	51	M	Anomalous right pulmonary venous drainage into inferior vena cava; hypoplastic right pulmonary artery; probable atrial septal defect	Dextrorotation of heart; anomalous pulmonary artery into inferior vena cava; hypoplastic right pulmonary artery; probable atrial septal defect	Electrocardiographic changes (right axis deviation and incomplete bundle branch block) suggested atrial septal defect, but cardiac catheterization was refused by the patient because he was asymptomatic (previously published[26])

TABLE I (*Continued*)

Case No.	Age (yr.)	Sex	Associated Anomalies and Disease	Findings	Remarks
26	45	M	Anomalous right pulmonary venous drainage into inferior vena cava	None	Classic dextrorotation of heart and anomalous pulmonary venous drainage pattern into inferior vena cava seen on conventional roentgenogram (Fig. 10); laminectomy for cervical spondylosis prevented angiocardiographic studies
27	16	M	Pulmonic stenosis; ventricular septal defect (tetralogy of Fallot); scoliosis of spine	Dextrorotation of heart; pulmonic stenosis; ventricular septal defect	Refused cardiac catheterization
28	7	F	Persistent left superior vena cava; ostium primum	Dextrorotation of heart; left-to-right shunt at atrioventricular level	Cardiac catheterization clearly demonstrated left-to-right shunt at atrioventricular level
29	12	F	Ostium primum	Dextrorotation of heart; left-to-right shunt at ventricular level	Vector electrocardiography and cardiac catheterization favored diagnosis of ostium primum
30	69	M	Atrial septal defect	Dextrorotation; huge right ventricle, pulmonary artery and branches; left-to-right shunt at atrial level	Referred because of huge heart in right thorax; had greatly calcified pulmonary arteries
31	18	F	Pulmonic stenosis; atrial septal defect with right-to-left shunt	Atrial septal defect with right-to-left shunt and pulmonic stenosis	Referred because of enlarged heart and murmurs; conventional roentgenograms and angiocardiograms recently published[3]
32	6 wk.	M	Ventricular septal defect	Left-to-right shunt due to ventricular septal defect and cardiac chamber enlargement owing to heart failure	Autopsy following cardiac arrest during banding of pulmonary artery confirmed angiocardiographic findings
33	16 mo.	F	Ostium primum; mitral insufficiency; mild tricuspid stenosis; persistent left superior vena cava	Left superior vena cava and left-to-right shunt at ventricular level	Cardiac catheterization showed bidirectional shunting at atrioventricular level
34	3 mo.	F	Pulmonic stenosis; hypoplastic right pulmonary artery; ventricular septal defect; anomalous arteries of abdominal aorta into right lower lung; synostosis of ribs; hemivertebrae	Pulmonic valvular stenosis; hypoplastic right pulmonary artery; anomalous abdominal aortic branches to right lower lobe	Cyanotic since birth; died 3 mo. later; autopsy confirmed angiocardiographic findings
35	3½ wk.	F	Patent ductus arteriosus; ventricular septal defect; 17–18 trisomy syndrome	Blanching sign in left pulmonary artery with left-to-right shunt; reopacification of right cardiac structures and left pulmonary artery; ductus also visualized via retrograde aortography	Patent ductus arteriosus ligated on 2/26/63; patient doing well
(a) Corrected Transposition					
36	8	F	Corrected transposition; tetralogy of Fallot	Pulmonic valvular stenosis; ventricular septal defect; corrected transposition	Died at age 16 years, no autopsy; cardiac catheterization established ventricular septal defect and pulmonic stenosis
37	22	F	Corrected transposition; eventration of left diaphragm; pseudocoarctation of aorta	Dextrorotation; corrected transposition; pseudocoarctation	Asymptomatic; pre-employment roentgenogram was followed by angiocardiography (previously published[27])
38	3 mo.	M	Corrected transposition; ventricular septal defect; pulmonary atresia	Corrected transposition; dextrorotation; pulmonary atresia; ventricular septal defect	Angiocardiographic findings confirmed at autopsy (previously published[3])

Table I (*Continued*)

Case No.	Age (yr.)	Sex	Associated Anomalies and Disease	Findings	Remarks
39	4	F	Corrected transposition	Normal-sized cardiac chambers in classic corrected transposition (Fig. 11, *B* and *C*)	Referred because of heart murmur after birth
40	3 da.	M	Corrected transposition; pulmonary atresia; atrial septal defect	Dextrorotation; pulmonary atresia; corrected transposition	Cyanotic and dyspneic patient died suddenly at home 2 wk. after study; no autopsy
41	14	M	Corrected transposition; mild pulmonic stenosis; complete heart block	Corrected transposition; pulmonic valvular stenosis; dextrorotation	Intrapericardial-aortopulmonary shunt improved patient
42	6	M	Corrected transposition	Mild dextrorotation; classic corrected transposition	Murmurs on physical examination led to study
43	16	M	Corrected transposition; mild subvalvular pulmonic stenosis; atrial septal defect	Classic dextrorotation; corrected transposition (Fig. 12, *B*, *C*, *D* and *E*)	Atrial septal defect repaired; pulmonic valve explored and found normal; mild subvalvular pulmonic stenosis did not require surgery; doing well—2 year follow-up
44	14	M	Corrected transposition with "mitral" stenosis; cardiac arrythmia (shifting pacemaker with heart block)	Dextrorotation of heart; corrected transposition; large long-opacified left atrium	Died suddenly at home, no autopsy; stenosis of systemic atrium equivalent to a "left-sided" Ebstein's anomaly of tricuspid valve
45	9	F	Corrected transposition; pulmonic stenosis; ventricular septal defect (tetralogy of Fallot)	Classic corrected transposition with right-to-left shunt at ventricular level; pulmonic stenosis	Cyanotic since birth; operation advised
46	5	M	Corrected transposition; ventricular septal defect; patent foramen ovale	Dextrorotation of heart; large right ventricle, pulmonary artery, and left atrium (Fig. 13, *B*, *C*, *D* and *E*)	Pulmonary artery could not be catheterized but a ventricular septal defect and a patent foramen ovale were demonstrated
(b) Dextrocardia, Corrected Transposition, and Situs Inversus					
47	6	F	Dextrocardia; corrected transposition; atrial septal defect; pulmonary stenosis; situs inversus	Dextrorotation; dextrocardia; corrected transposition	"Levocardia"; when roentgenogram was reversed, appeared as dextrorotation
48	16	M	Corrected transposition; situs inversus; persistent "left" superior vena cava	Left superior vena cava; large pulmonary artery; corrected transposition; dextrocardia	
49	4½	M	Dextrocardia; corrected transposition; bilateral superior venae cavae with right draining into left atrium; pulmonary valvular stenosis; situs inversus	Dextrocardia; corrected transposition; pulmonic stenosis; right superior vena cava draining into left atrium and left superior vena cava draining into right atrium	Severely cyanotic and dyspneic; improved after aortico-pulmonary artery (Blalock-Taussig) shunt

The degree of frontal plane displacement varies from mild rotation in a case unassociated with cardiac anomalies (Fig. 3, *A* and *B*) to marked displacement (Fig. 4, *A–D*) such as in a patient with enlargement of the heart due to acquired rheumatic heart disease and mitral stenosis. Dextrorotation of the heart, acquired mitral stenosis, persistent left superior vena cava, and an absent left kidney were also recently reported by Schreiner and Lyons.[19] However, some patients with normally sized hearts may have so little right-sided displacement in the frontal view, although the ventricles lie side by side in the transverse plane, that the term mesorotation has been used.[3] Actually, it is a lesser degree of dextrorotation.

Eighty per cent of the patients in this series had associated cardiovascular anom-

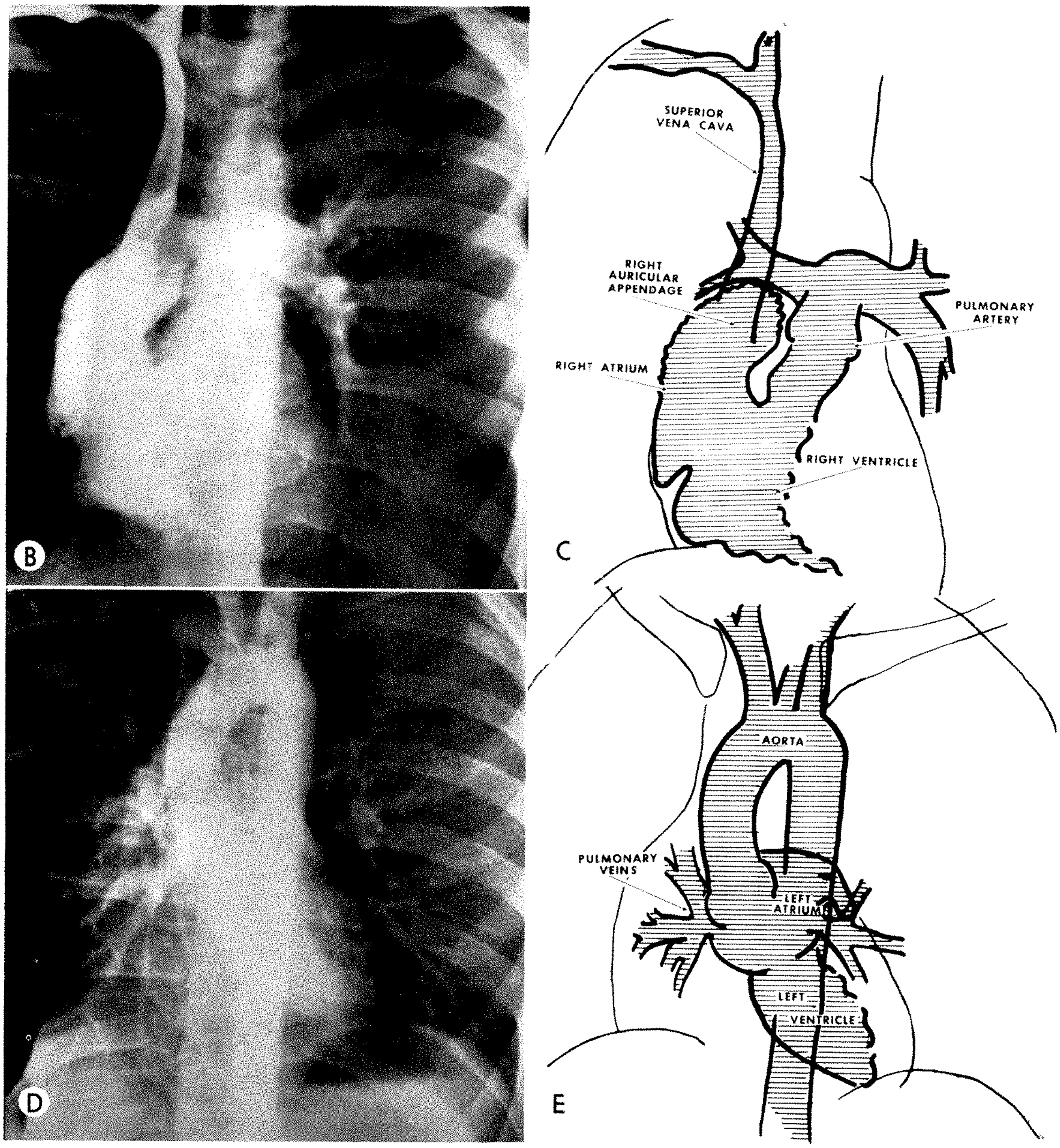


Fig. 1. (*B*) Frontal teleangiocardiogram revealing mild dextrorotation of the right atrium and ventricle. The pulmonary artery is medially placed. (*C*) Tracing of *B*. (*D*) Frontal teleangiocardiogram showing dextrorotation of the left atrium, ventricle, and aorta. The ventricular septum is perpendicular to the frontal plane and displaced to the right. The aorta is unfolded—as in the left anterior oblique position. (*E*) Tracing of *D*.

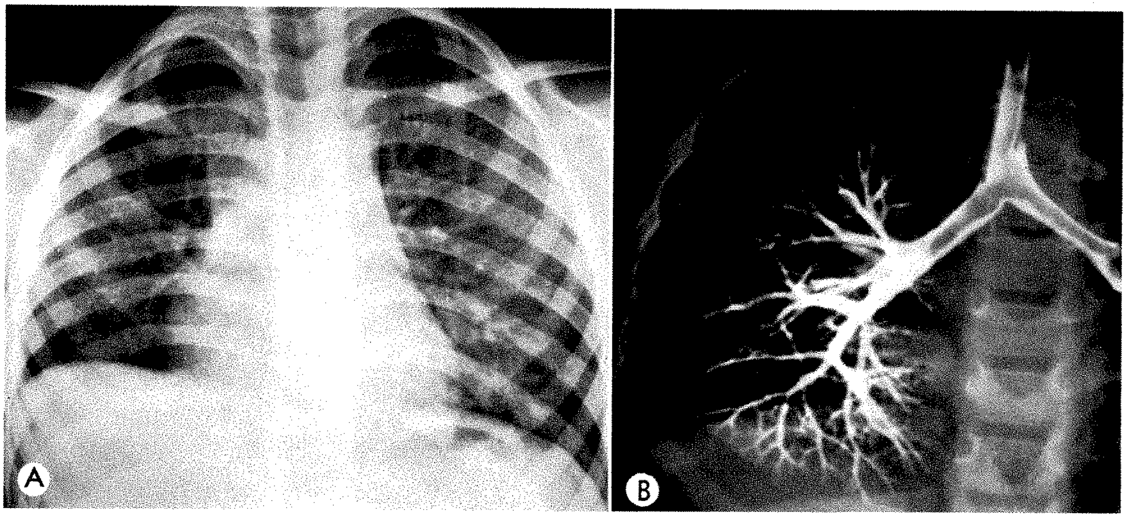


FIG. 2. Case 5. *Dextrorotation of the heart without associated cardiovascular anomalies, but with absence of the right upper lobe.* (*A*) Conventional teleroentgenogram showing unusual prominence of the right cardiac silhouette. (*B*) Bronchogram demonstrating congenital absence of the right upper lobe.

alies (Table I). Congenital absence of the right pulmonary artery was present in 2 patients (Cases 11 and 12) (Fig. 5, *A* and *B;* and 6, *A–E*). In both, abnormalities of the right bronchial tree were present (Fig. 6, *B* and *C*). One of these patients also had a large right pulmonary artery (bronchial) arising from the descending thoracic aorta (Fig. 6*E*). Hypoplasia of the right pulmonary artery as an isolated associated lesion was noted in 2 instances (Cases 14 and 15), but more commonly a hypoplastic right pulmonary artery was associated with other anomalies such as aberrant arteries from the abdominal aorta into the right lower lobe (Case 13) (Fig. 7, *B*, *C* and *D*) and anomalous pulmonary venous drainage of the right lung into the inferior vena cava. The latter abnormality was found in 10 patients, with and without aberrant arteries from the abdominal aorta (Cases 17 to 26) (Fig. 8 through 10, inclusive).[24,26] Dextrorotation rather than dextroposition of the heart was noted in these cases despite recent reports to the contrary.[10,15]

In 13 patients, dextrorotation of the heart was associated with corrected transposition.[1,6,9] In the latter condition, the aorta arises anteriorly and lateral to the posterior and medial pulmonary artery; the ascending aorta produces a prominent shadow along the left upper cardiac border and hilus. It then turns medially and descends normally (Fig. 11 through 13, inclusive). This orientation of the great vessels is usually associated with ventricular inversion (the venous ventricle is a morphologic left ventricle and has a bicuspid atrioventricular valve; the arterial ventricle is a morphologic right ventricle with tricuspid valve). When cardiac chamber enlargements exist because of septal and/or valvular defects, the changes are even more striking (Fig. 13, *A–E*).

In 3 patients (Cases 47 to 49), the triad of mirror-image dextrocardia and situs inversus, corrected transposition of the great vessels, and dextrorotation was present. In the last patient (Case 49) anomalous drainage of the right superior vena cava into the left atrium, pulmonic stenosis, and a ventricular septal defect were also present. The basic pattern of mirror-image dextrocardia (venae cavae on the left, apex on the right) was complicated by rotation in the frontal and transverse

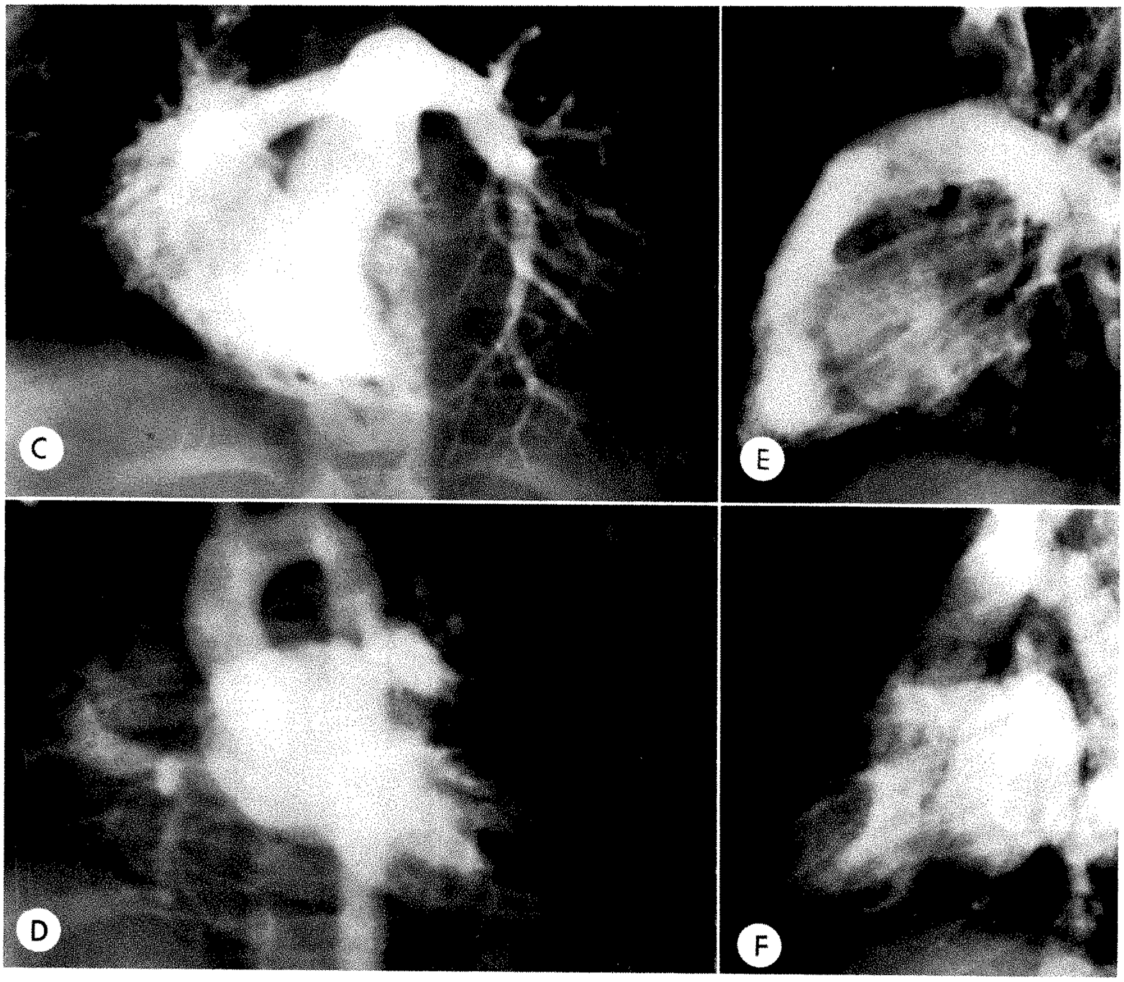


Fig. 2. (*C*) Frontal angiocardiogram revealing that the dextrorotated right atrium and ventricle are responsible for the prominent right border of the cardiac silhouette. (*D*) Frontal angiocardiogram demonstrating left cardiac chamber dextrorotation and unfolding of the aorta. (*E*) Lateral (biplane of *C*) angiocardiogram of the right heart chambers and pulmonary arterial system. (*F*) Lateral (biplane of *D*) angiocardiogram of the left atrium, ventricle, and aorta.

plane, typical of dextrorotation. Since the right-sided heart mirror-image dextrocardia was actually rotated to the left (the opposite of dextrorotation in a normally situated heart), this anomaly should correctly be termed mirrior-image dextrorotation with levorotation or "levocardia." The understanding of this anomaly is enhanced if the chest roentgenogram is reversed; the mirror-image dextrocardia is then eliminated and the cardiac silhouette resembles dextrorotation with corrected transposition in a normally situated heart.[3]

DISCUSSION

Dextrorotation is a morphologic entity produced by a specific defect in embryogenesis. During the sixth week of fetal life, the heart begins to attain its mature external configuration and descends from the cervical region to its permanent location in the thorax. At the same time it rotates into the left hemithorax. Important changes then occur. The spiral conotruncal septum separates the pulmonary artery from the aorta and the primitive bulbus becomes absorbed into the right ventricle, the

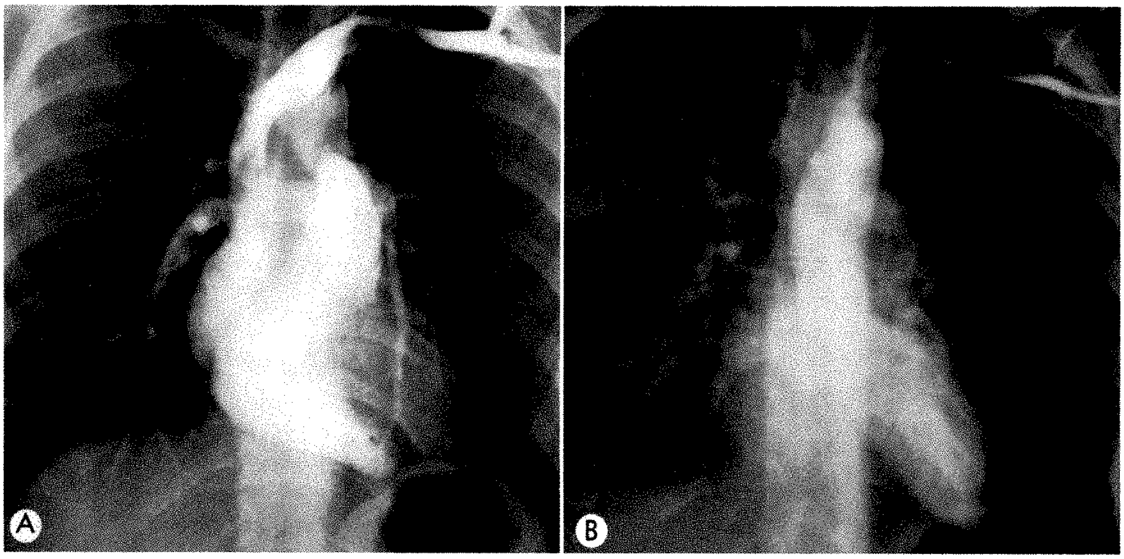


FIG. 3. Case 6. *Dextrorotation without associated cardiovascular anomalies.* (*A*) Frontal angiocardiogram showing a mild degree of dextrorotation; the medially placed pulsatile pulmonary artery simulates pulmonary artery enlargement. (*B*) Frontal angiocardiogram showing the mildly dextrorotated left heart structure. This mild degree of dextrorotation has been termed mesorotation. However, it is merely a minor degree of dextrorotation.

ventricular and atrial septa become differentiated, the sinus venosus and systemic veins become part of the right atrium, and the pulmonary veins unite with the left atrium. In addition, the splenic anlage is formed, the septum transversum reaches its definitive position and unites with the pleuroperitoneal membrane to form the diaphragm, the cartilaginous sternum develops, and the primitive lung buds subdivide into the bronchial tree. This cluster of important embryonic events between the sixth and eighth weeks of fetal life makes this period an especially vulnerable time for the occurrence of multiple congenital anomalies. A teratogenic agent acting at this time may prevent the primitive heart from reaching its definitive position in the left hemithorax, thus producing cardiac and extracardiac malformations.[3]

These developmental considerations suggest that the extracardiac anomalies frequently seen in dextrorotation may not be mechanical causes of malrotation but rather are associated malformations probably resulting from the same teratogenic insult. If these extracardiac defects were mechanical causes of dextrorotation, then malrotation would be more commonly found in patients with these defects. Dextrorotation, however, is only rarely seen with pectus excavatum and is not too frequent in cases of eventration of the diaphragm. Dextrorotation has been observed with eventration of either the left or right diaphragm. It is difficult to see how defects could produce an identical malrotation of the heart on a solely mechanical basis.[3]

Spitzer[21] pointed out in 1923 that transposition of the great vessels was common in dextrorotation. Grant[11] confirmed this and demonstrated that this was not the passive result of the rotation since this would have opened the aortic loop. Arcilla and Gasul,[2] however, felt that transposition was usually incorrectly diagnosed in this anomaly and suggested that the aorta always originated to the left and anterior to the pulmonary artery in dextrorotation. Ten patients in the present series and one illustrated by Grant had the conotruncal anomaly, first described by Rokitansky and

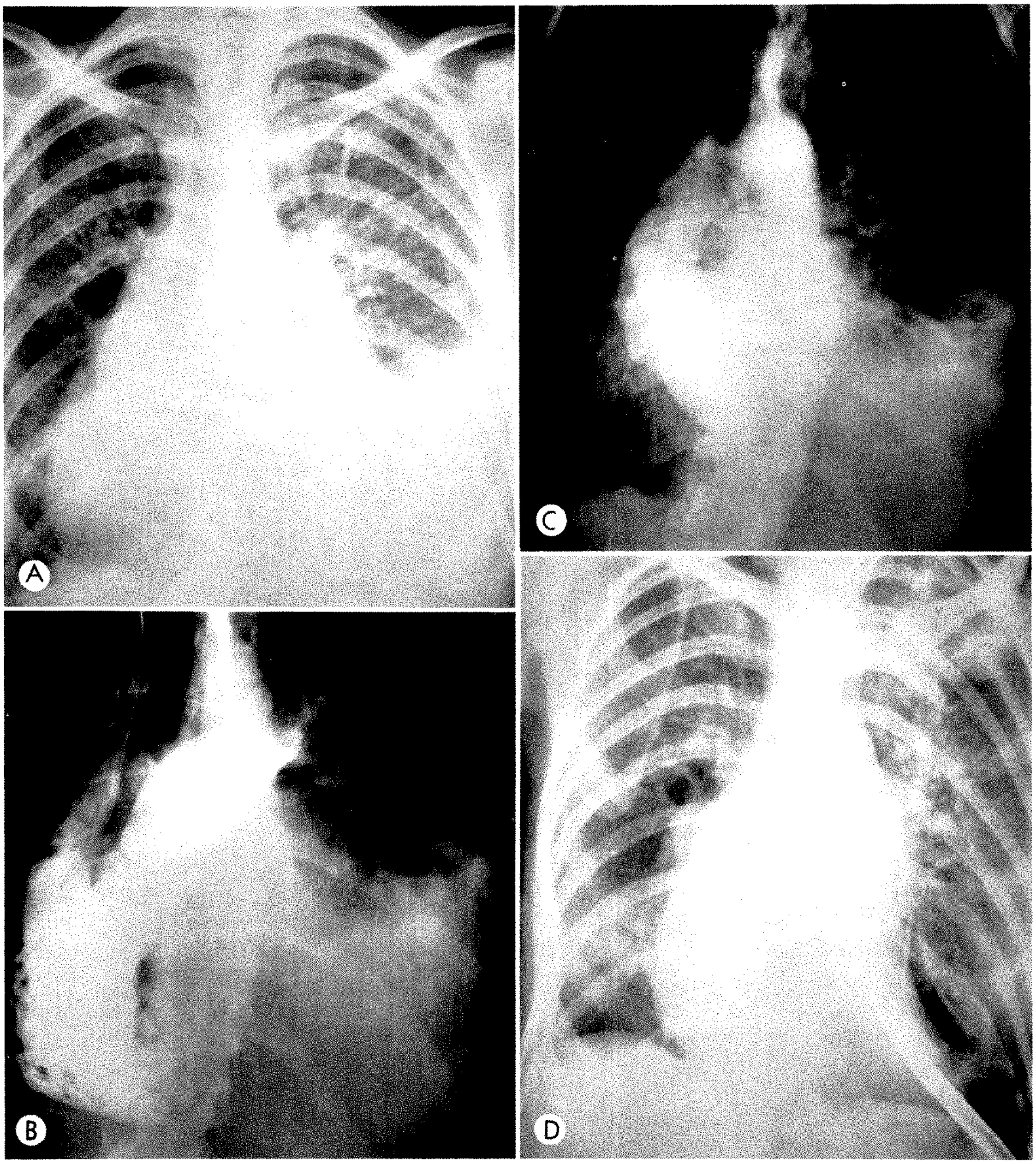


FIG. 4. Case 10. *Dextrorotation of the heart in a patient with rheumatic mitral stenosis.* (*A*) Conventional teleroentgenogram showing an enlarged heart extending well into the right hemithorax. The left pleural effusion at first was thought to be responsible for the cardiac displacement (dextroposition). (*B*) Frontal angiocardiogram showing that the enlarged right heart structures are dextrorotated. (*C*) When the left heart was visualized, the large left atrium, the ventricle, and aorta were also dextrorotated. (*D*) Postoperative frontal roentgenogram after mitral valvulotomy showing drainage of the left pleural effusion by a tube in the pleural cavity but the heart remains in the dextrorotated position, proving that the left pleural effusion was not the cause of the cardiac shift into the right hemithorax.

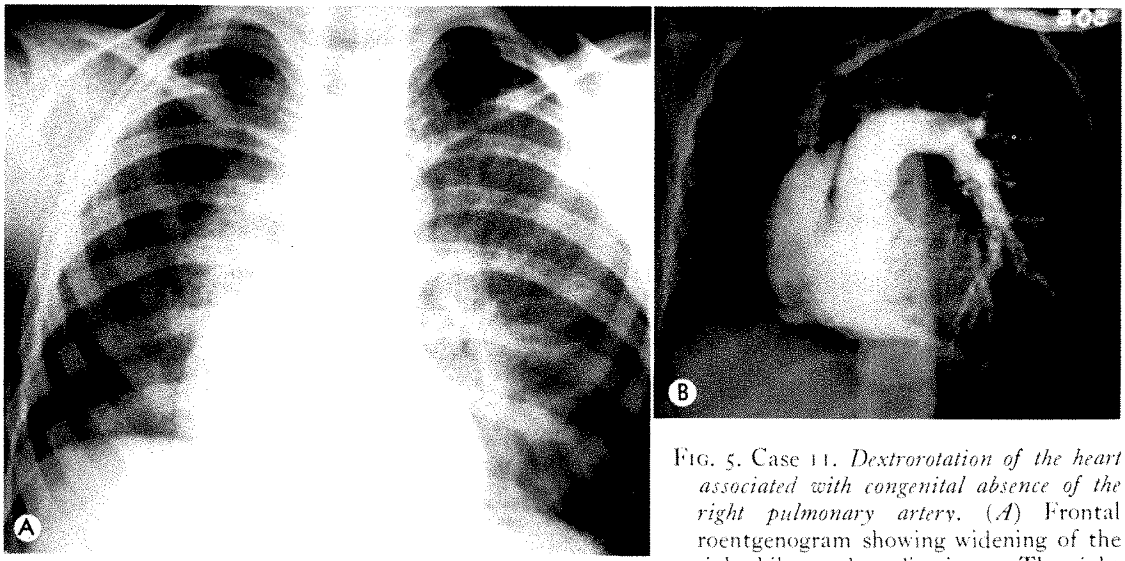


Fig. 5. Case 11. *Dextrorotation of the heart associated with congenital absence of the right pulmonary artery.* (*A*) Frontal roentgenogram showing widening of the right hilus and mediastinum. The right lung is smaller than the left and the right pulmonary vasculature is absent. (*B*) Frontal angiocardiogram revealing dextrorotation of the heart structures and congenital absence of the right pulmonary artery.

more recently by Anderson, Lillehei and Lester[1] as corrected transposition of the great vessels. The important differential point is evident on the frontal angiocardiogram; with a normal aortic root, the loop is wide and the ascending aorta arises convexly to the right (Fig. 1, *D* and *E*). In corrected transposition the ascending aorta arises convexly to the left and forms a prominent portion of the left upper cardiac border and hilus (Fig. 11*C*, 12*C*, and 13*C*). An explanation for the common association of corrected transposition and dextrorotation may be found in the theory of de la Cruz and associates,[6] who have postulated that corrected transposition in a normally situated heart results from complete inversion of the bulbo-ventricular loop and failure of the loop to rotate into the right hemithorax. They suggest that if the inverted loop rotates into the right hemi-

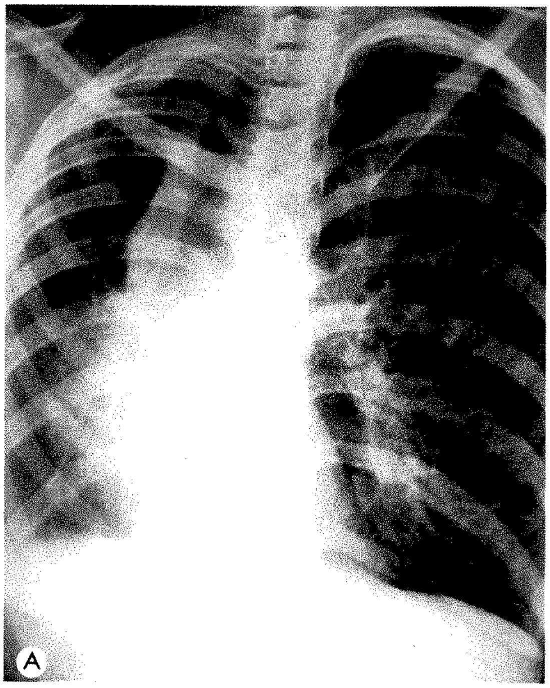


Fig. 6. Case 12. *Dextrorotation of the heart associated with congenital absence of the right pulmonary artery, right pulmonary artery (bronchial artery) arising from the descending aorta, and malformation and bronchiectasis of the right lung bronchi.* (*A*) Conventional teleroentgenogram showing the malposition of the heart into the right hemithorax, right mediastinal herniation, and markedly decreased right lung and vasculature.

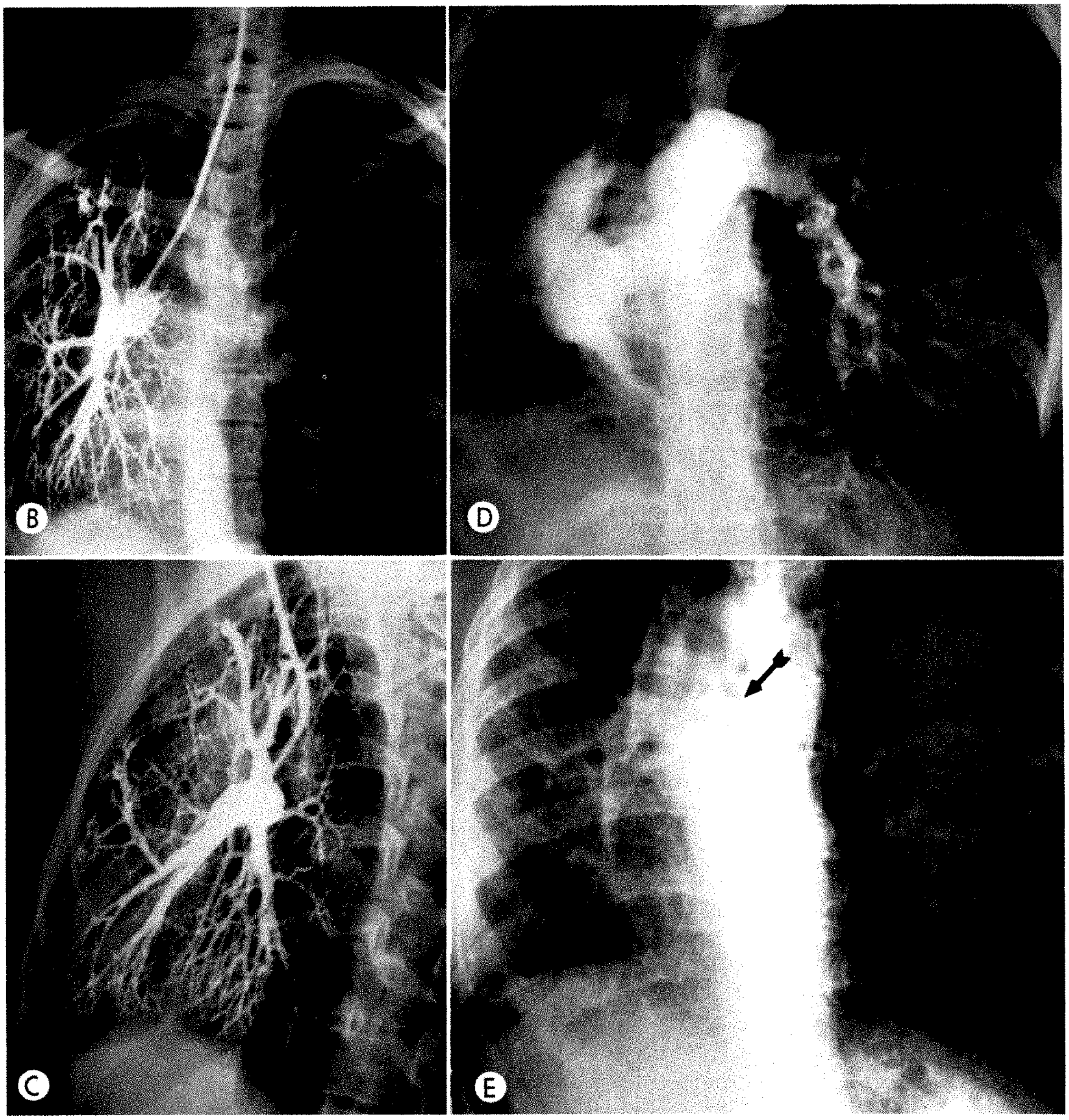


FIG. 6. (*B*) Frontal bronchogram demonstrating the deformed right bronchial tree with bronchiectasis of the upper lobe. (*C*) Oblique bronchogram better revealing the deformed and diseased right bronchial system. (*D*) Frontal angiocardiogram disclosing dextrorotation of the heart and congenital absence of the right pulmonary artery. (*E*) When the left side of the heart was opacified, a large trunk (bronchial artery) was seen arising from the descending portion of the aorta (arrow).

thorax, dextrorotation and corrected transposition result. If this explanation is correct, then the combined defect of dextrorotation and corrected transposition results from a teratogenic agent acting on the embryonic heart before the straight cardiac tubes develop the sigmoid twist (third week of fetal life).

Despite the many and confusing classifications of dextrocardia,[2] the differentiation of dextrorotation from dextrocardia is usually not difficult. In this report the classification of right-sided hearts is simplified. Dextrorotation is defined as a morphologic entity and the associated thoracic deformities are considered to be part of the mal-

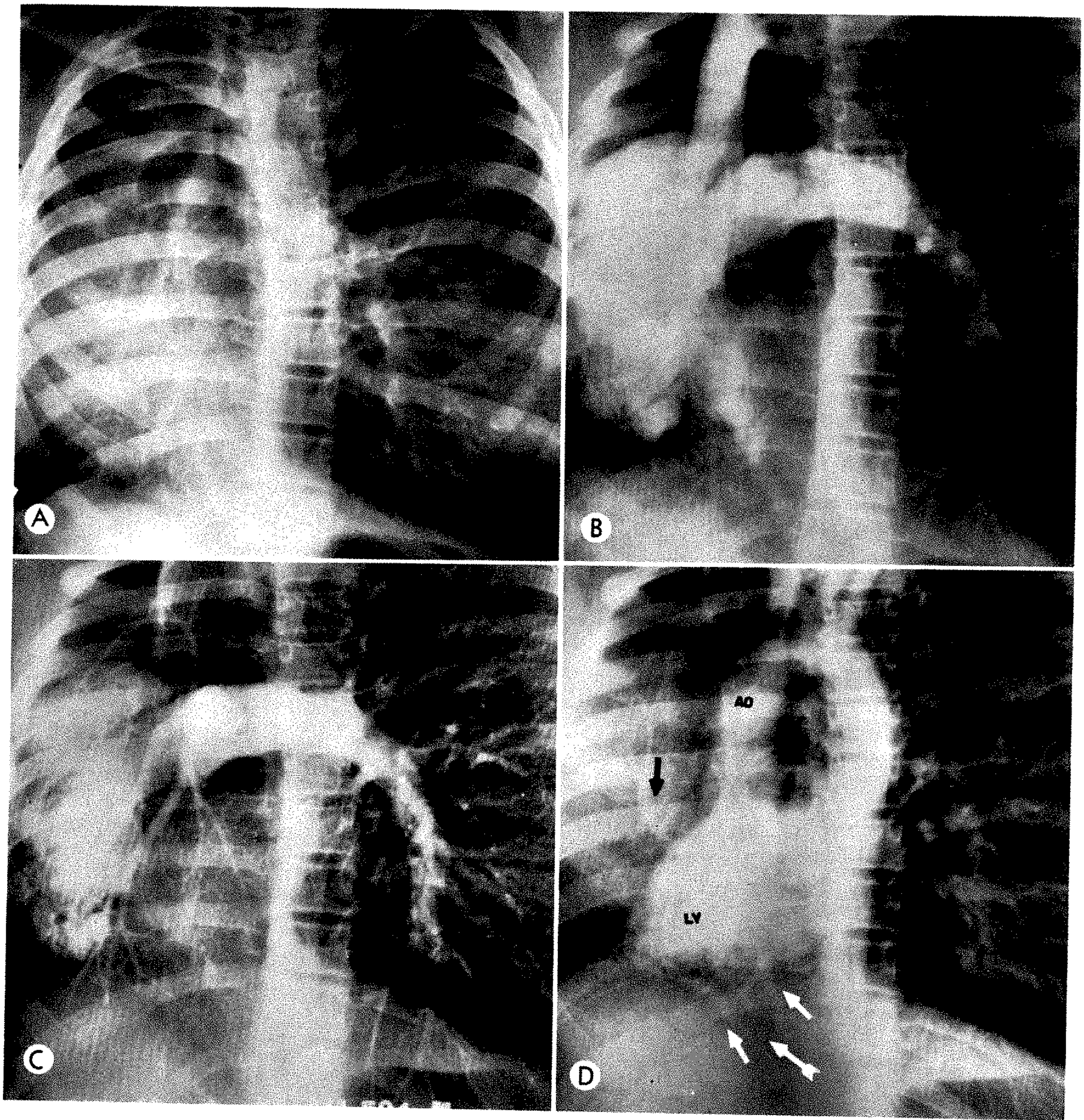


FIG. 7. Case 13. *Dextrorotation, hypoplastic right pulmonary artery, and systemic arteries from the abdominal aorta inserting into the right lower lobe.* (*A*) Frontal teleroentgenogram showing a dense right hemithorax. (*B*) Frontal angiocardiogram showing dextrorotation of the right heart chambers. The superior vena cava and pulmonary artery are also rotated towards the right hemithorax. (*C*) The hypoplastic left pulmonary artery and the distortion and meagerness of the right pulmonary arterial tree are evident. (*D*) When the left ventricle and aorta were opacified, three arteries (lower arrows) from the abdominal aorta drained into the right lower lobe. Upper arrow points to the hypoplastic pulmonary veins; AO is the aorta markedly unfolded owing to dextrorotation of the cardiovascular structure; LV is the left ventricle. (Reproduced by permission from the *American Journal of Surgery*.)

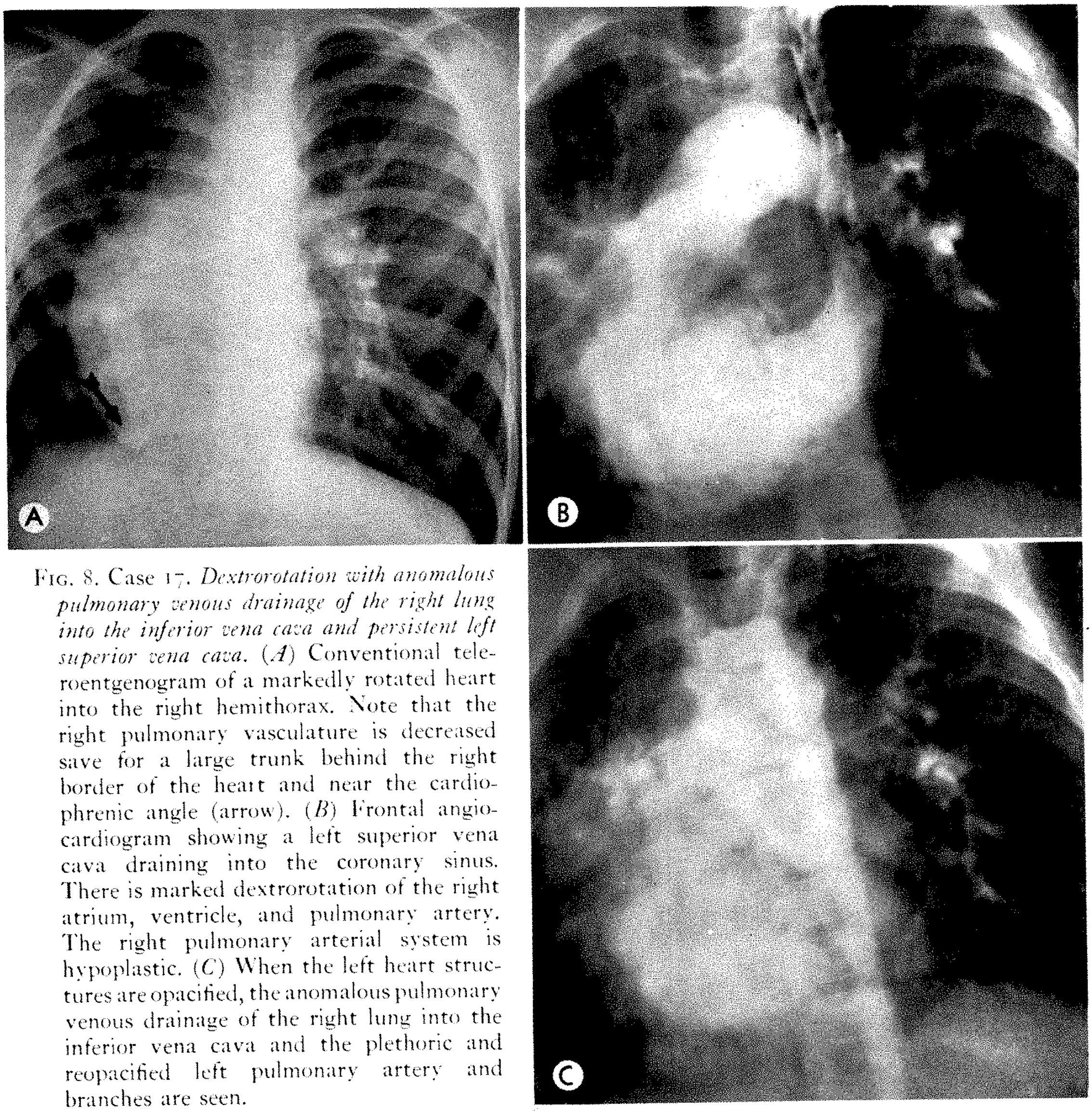


Fig. 8. Case 17. *Dextrorotation with anomalous pulmonary venous drainage of the right lung into the inferior vena cava and persistent left superior vena cava.* (*A*) Conventional teleroentgenogram of a markedly rotated heart into the right hemithorax. Note that the right pulmonary vasculature is decreased save for a large trunk behind the right border of the heart and near the cardiophrenic angle (arrow). (*B*) Frontal angiocardiogram showing a left superior vena cava draining into the coronary sinus. There is marked dextrorotation of the right atrium, ventricle, and pulmonary artery. The right pulmonary arterial system is hypoplastic. (*C*) When the left heart structures are opacified, the anomalous pulmonary venous drainage of the right lung into the inferior vena cava and the plethoric and reopacified left pulmonary artery and branches are seen.

formation. In the classic case of dextrocardia, there is associated complete situs inversus; the location of the stomach bubble under the right diaphragm is a valuable aid in diagnosis.[13] This can be confirmed by remembering that the cardiac silhouette in dextrocardia is a perfect mirror-image and that if the chest roentgenogram is reversed or the patient is roentgenoscoped from the back, *i.e.*, posteroanteriorly, completely normal relationship will be demonstrated. Angiocardiography needs rarely to be performed in patients with dextrocardia. Only 3 patients with complicating rheumatic heart disease and mitral stenosis have been studied angiocardiographically in this center.[20]

Figure 14, *A–D* illustrates such a case, in which differentiation of dextroposition from dextrorotation (dextroversion) of the heart was made (Case 10). A patient with left-sided pleural effusion complicating rheumatic heart disease and mitral stenosis showed marked malrotation of the heart into the right hemithorax (Fig. 4*A*). However, angiocardiography demonstrated dextro-

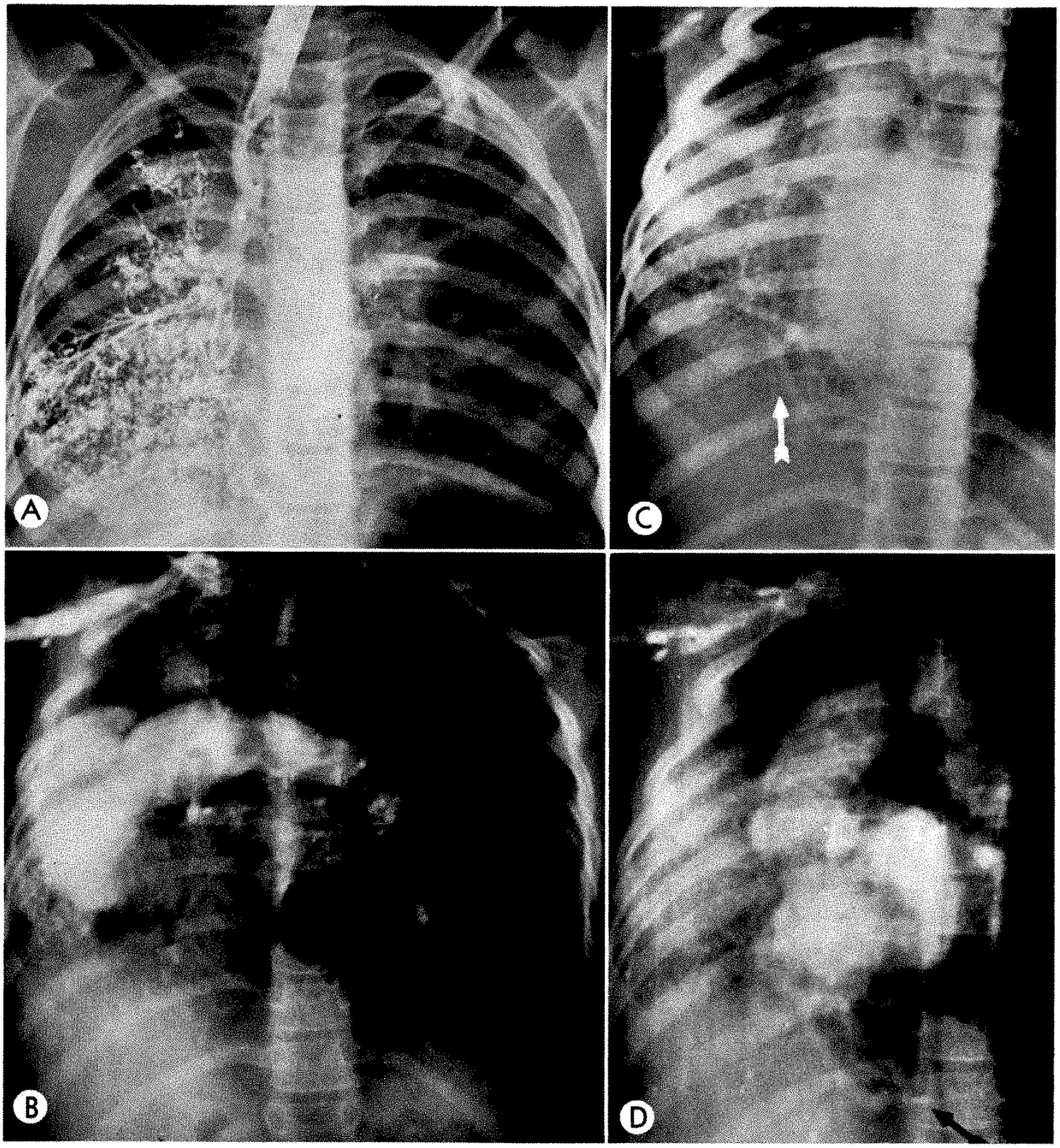
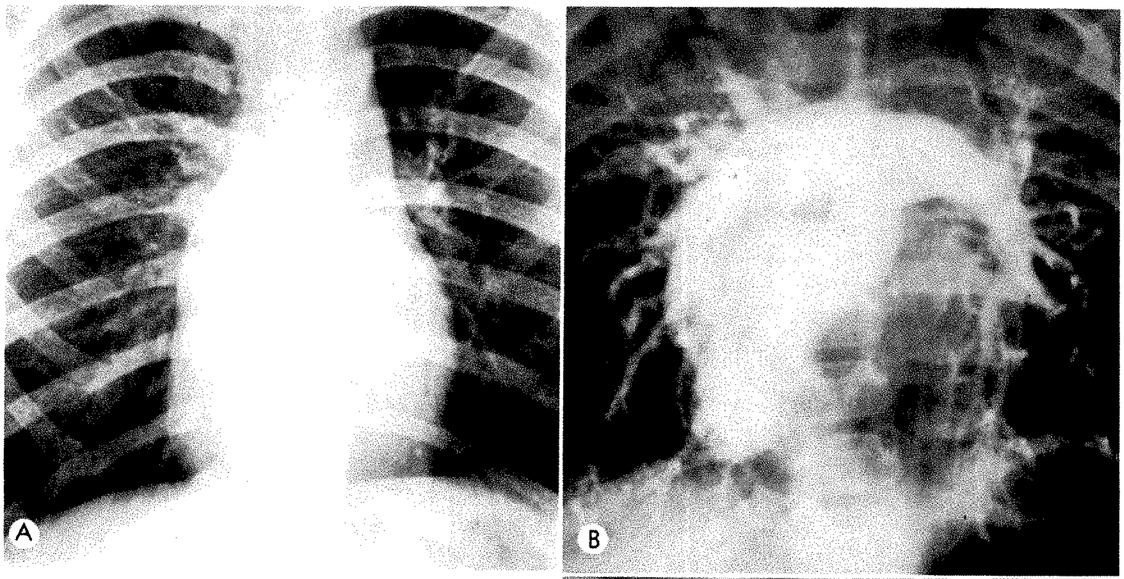


Fig. 9. Case 18. *Dextrorotation with anomalous pulmonary venous drainage of the right lung into the inferior vena cava, hypoplastic pulmonary artery, systemic arteries from abdominal aorta to right lower lobe, and malformation of the right bronchial tree.* (*A*) Frontal right bronchogram showing bizarre malformations of the right bronchial tree. (*B*) Frontal angiocardiogram showing pronounced dextrorotation of the heart and hypoplasia of the right pulmonary artery. (*C*) When the left heart structures were opacified, an anomalous vein draining into the inferior vena cava and a series of arteries (arrow) from the abdominal aorta into the right lower lobe were demonstrated. (*D*) Intravenous abdominal aortogram showing the anomalous branches from the abdominal aorta (arrow).



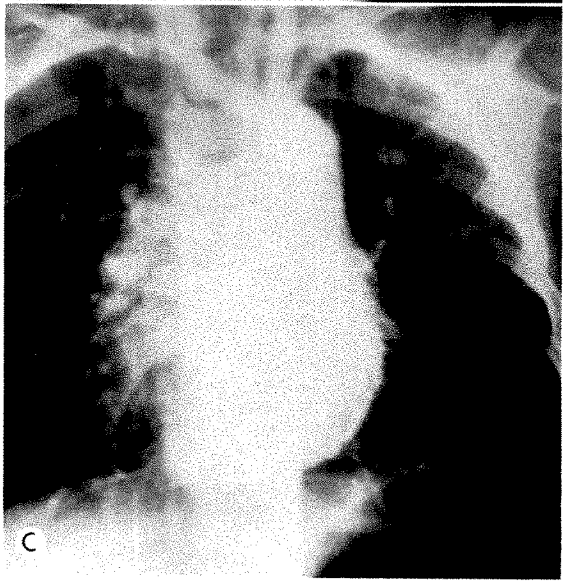


FIG. 11. Case 39. *Dextrorotation with corrected transposition.* (*A*) Conventional teleroentgenogram showing displacement of the heart towards the right hemithorax and prominence of the left upper hilus shadow. (*B*) Frontal angiocardiogram revealing the characteristic features of dextrorotation of the heart with a centrally placed pulmonary artery and branches. The venous right heart chamber has the contour of a "left" ventricle. (*C*) Left heart frontal angiocardiogram showing the trabeculation of the left ventricle which has the appearance of a "right" ventricle. Both the ascending and descending portions of the aorta lie along the left border of the spine.

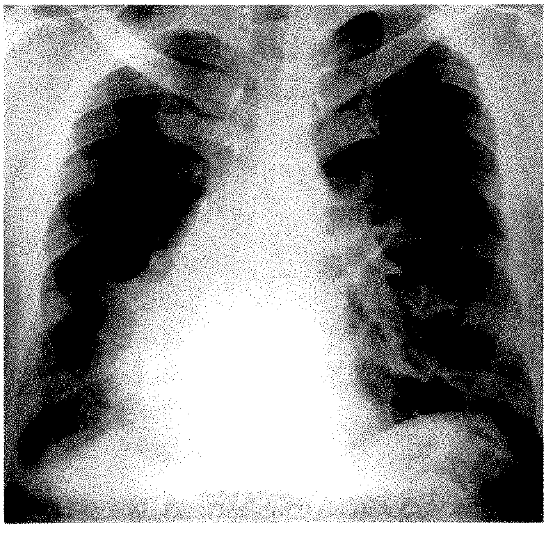


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FIG. 10. Case 26. *Conventional roentgenogram showing dextrorotation and the classic features of anomalous pulmonary venous drainage of the right lung into the inferior vena cava.* Frontal teleroentgenogram shows malrotation of the heart into the right hemithorax, a large vascular trunk near the right cardiophrenic angle, plethoric vasculature of an overdistended left lung, and poor vasculature of a hypoplastic right lung.

rotation of the heart in addition to mitral valvular disease (Fig. 4, *B* and *C*). Although mitral valvulotomy and drainage of the left pleural effusion were carried out (Fig. 4*D*), roentgenograms still demonstrated the heart in the dextrorotation position, proving that the left pleural effusion was not the cause of the malrotation.

Not all patients with congenital absence of a main branch of the pulmonary artery have dextrorotation of the heart.[17,22,25] A patient with congenital absence of the left pulmonary artery was recently observed (Fig. 15, *A*, *B* and *C*) but no dextrorotation was present. In cases of congenital absence of a main branch pulmonary artery, it is important to study the bronchi because congenitally malformed, partially absent, and bronchiectatic bronchi are not uncommon in this anomaly (Case 12) (Fig. 6, *A* and *B*). Anomalous pulmonary venous drainage of the right lung into the inferior vena cava is also commonly associated with congenitally malformed, partially absent, or infected bronchi (bronchiectasis) (Case 18) (Fig. 9*A*).[4,5,24,26] Accordingly, even though patients with dextrorotation of the heart do not have respiratory complaints, bronchographic studies should be done routinely. For instance, in Case 5 (Fig. 2*B*) bronchography was performed after dextrorotation of the heart was demonstrated and revealed congenital absence of the right upper lobe. Of course, bronchography is mandatory when there are respiratory complaints. Two patients (Cases 12 and 16) (Fig. 6, *B* and *C*) were found to have congenitally abnormal and secondarily infected bronchi.

When eventration of the left diaphragm is found, it is unwise to assume that the cardiac displacement is dextropositional.[12] Two patients in this series with anomalous pulmonary venous drainage of the right lung into the inferior vena cava also had eventration of the right diaphragm (Cases 23 and 24). In both patients an exploratory operation of the right hemithorax was performed; in the first case because a tumor mass was suspected,[24] in the other to correct the eventration of the diaphragm so that the right lung could be collapsed in preparation for repair of the coarctation of the aorta.[26] The operative findings confirmed those of the roentgenographic studies and in both instances the exploratory operations were unnecessary.

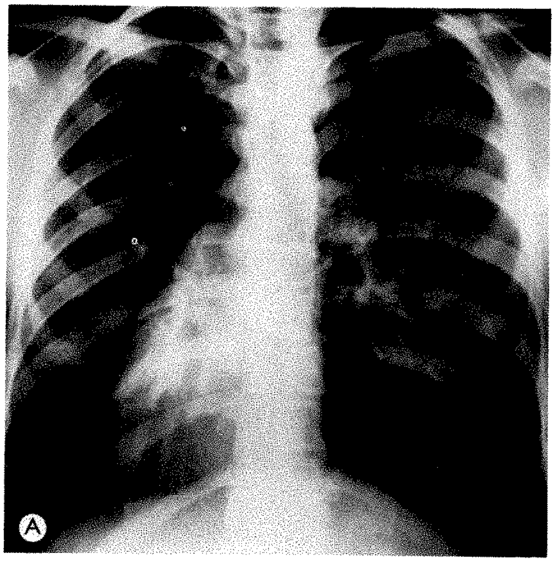

Fig. 12. Case 43. *Dextrorotation, corrected transposition, atrial septal defect, and mild subpulmonic stenosis.* (*A*) Conventional teleroentgenogram showing the left branch of the pulmonary artery in the left hilus; the aorta is obscured.

Two patients in this series had bronchial asthma (Cases 12 and 16). Case 12 (Fig. 6, *A–E*) had congenital absence of the right pulmonary artery and a congenitally malformed and bronchiectatic right bronchus. Case 16 had absence of the right upper lobe and hypoplasia of the right pulmonary artery. Both patients had reduced pulmonary function due to bronchospasm. Fortunately, both patients obtained relief with bronchodilators.

SUMMARY AND CONCLUSIONS

The roentgen finding of malrotation of the heart into the right hemithorax is of considerable clinical significance. Dextroposition, displacement of the heart into the right hemithorax, is usually easy to detect because adjacent disease of the lung, pleura or diaphragm can often be recognized at a

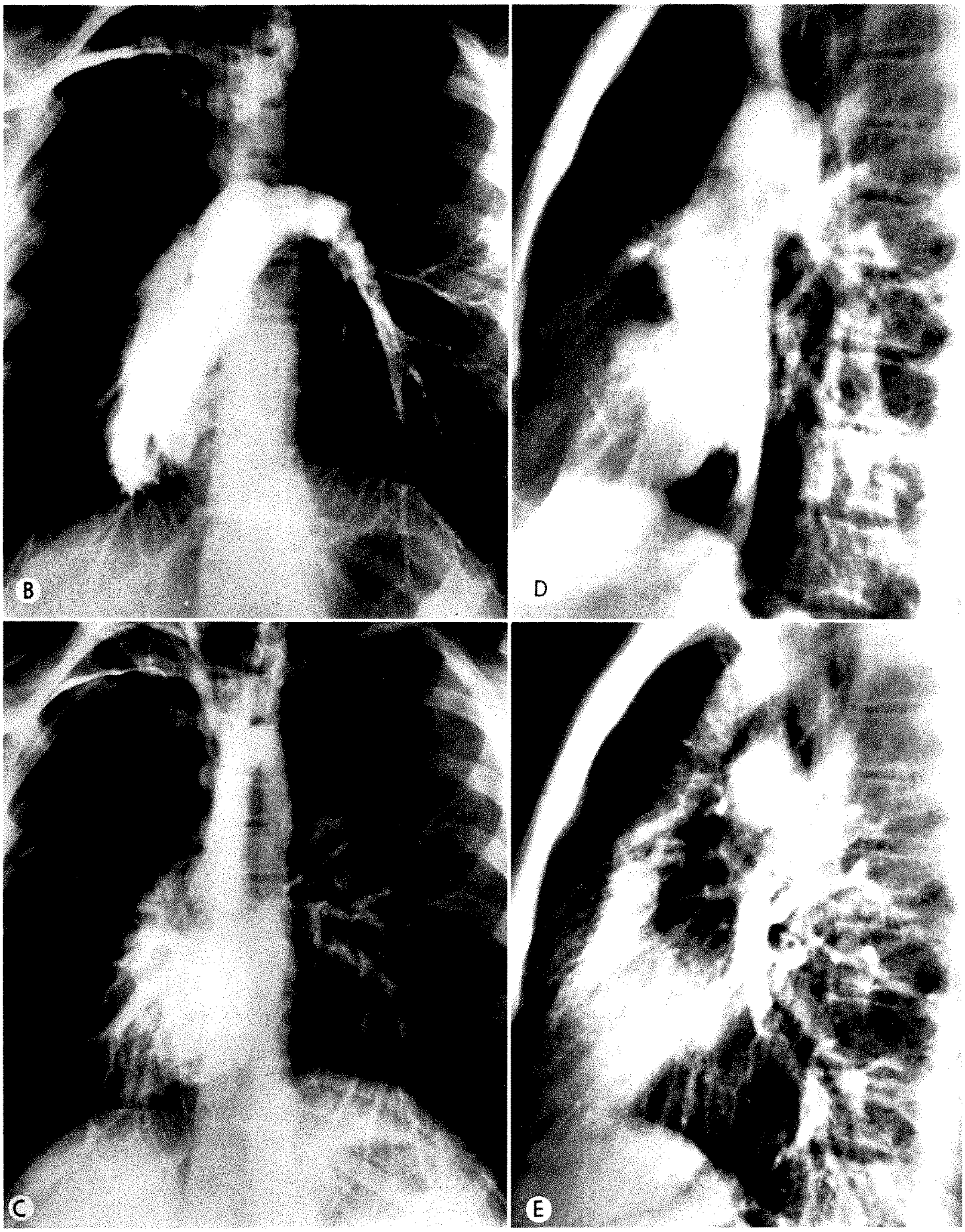

FIG. 12. (*B*) Frontal angiocardiogram showing the pronounced dextrorotated right heart structures and the enlarged medially placed pulmonary artery. (*C*) The left cardiac chambers are also dextrorotated but the aorta descends along the left border of the spine and there is little unfolding. (*D*) The lateral angiocardiogram of the right heart structures demonstrates the classic "right" ventricular pattern of the venous ventricle; the enlarged pulmonary artery is medial (biplane angiocardiogram of *B*). (*E*) Biplane angiocardiogram of *C* revealing the "left" ventricular appearance of the systemic ventricle. The aorta is anterior to the pulmonary artery.

glance. Similarly, mirror-image dextrocardia can also be diagnosed because there is almost always complete situs inversus and associated cardiovascular anomalies rarely occur. Reversal of the roentgenogram results in a completely normal cardiac silhouette. The diagnosis of dextrorotation or dextroversion is more difficult and minor degrees of dextrorotation may go undetected. Because many cardiovascular anomalies tend to occur with dextrorotation, special techniques, such as angiocardiography, cardiac catheterization, and vector electrocardiography analysis, may be necessary for a definitive diagnosis.

Dextrorotation apparently results from a teratogenic agent beginning in the sixth week of fetal life and at a time when the cardiovascular and respiratory system are being formed. Accordingly, associated anomalies of the cardiovascular and respiratory systems are common in dextrorotation. These cardiovascular anomalies are: anomalous pulmonary venous drainage of the right lung into the inferior vena cava; hypoplasia or absence of the right pulmonary artery; bronchial malformations and bronchiectasis of the right lung; absense of segments or lobes of the right lung; pleural and pericardial malformations; eventration of either of the diaphragms; and anomalous branches from the abdominal aorta to the right lower lobe. Corrected transposition, with and without cardiac shunts, apparently occurs in as many as 25 per cent of the cases of dextrorotation. Therefore, angiocardiography is important for diagnosis, while bronchography for detection of associated bronchopulmonary disease is essential.

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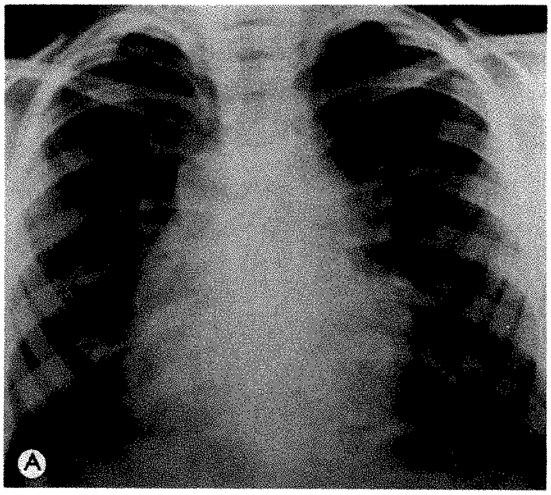

FIG. 13. Case 46. *Dextrorotation, corrected transposition, ventricular septal defect, and patent foramen ovale.* (*A*) Conventional teleroentgenogram showing an enlarged heart extending into the right hemithorax.

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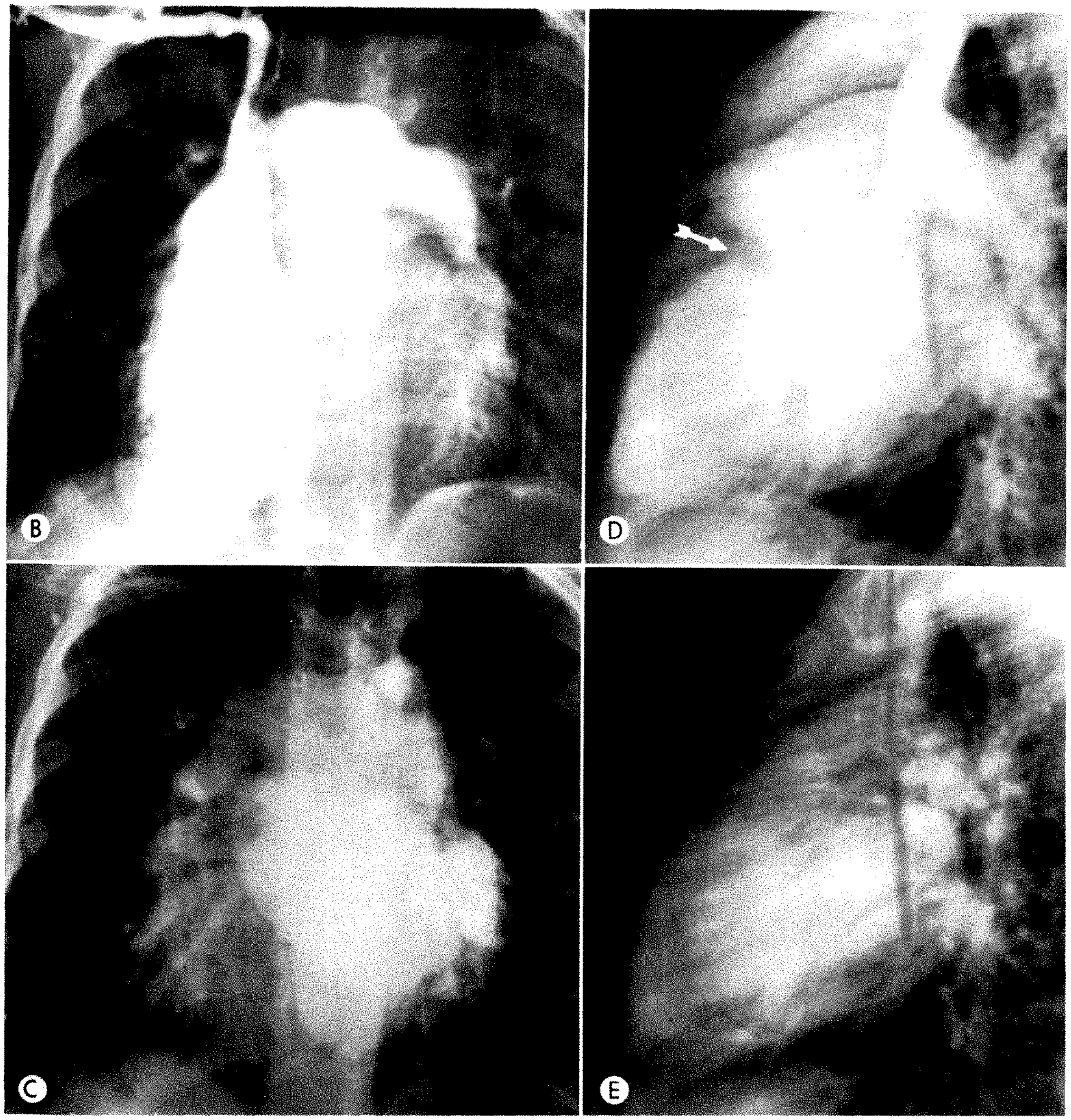

FIG. 13. (*B*) Frontal angiocardiogram revealing marked rotation and enlargement of the "right" (venous) ventricle and a centrally placed enlarged pulmonary artery. (*C*) Left heart frontal angiocardiogram demonstrating a huge "left" atrium and ventricle (systemic) with reopacification of the pulmonary artery. (*D*) Lateral angiocardiogram also showing the left ventricular pattern of the "right" (venous) ventricle. The groove between the pulmonary artery and the ventricle (arrow) is a common feature of corrected transposition. (*E*) Lateral angiocardiogram demonstrating the right ventricular appearance of the "left" (systemic) ventricle. The aorta is just anterior to the pulmonary artery (see *D*).

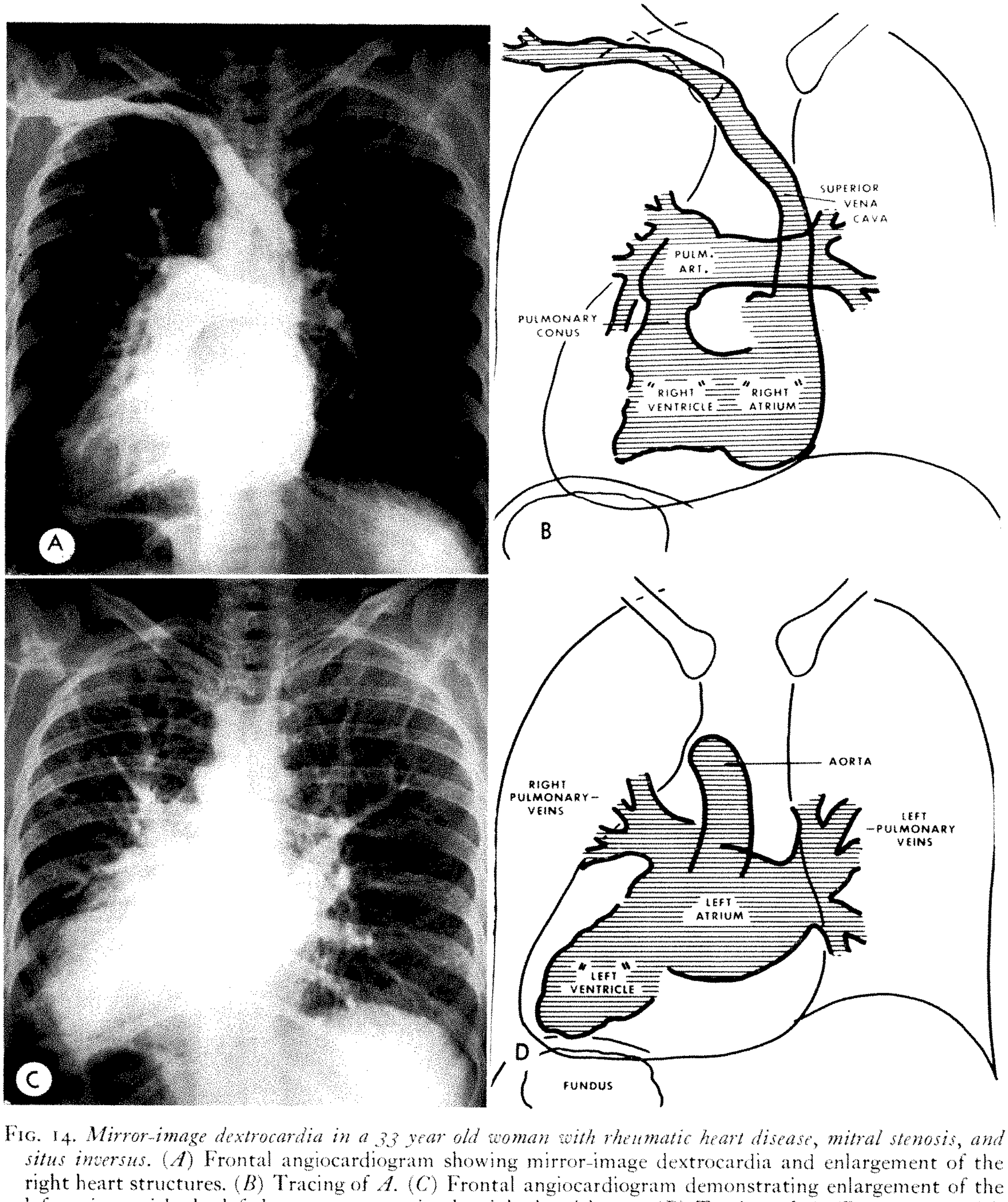

Fig. 14. *Mirror-image dextrocardia in a 33 year old woman with rheumatic heart disease, mitral stenosis, and situs inversus.* (*A*) Frontal angiocardiogram showing mirror-image dextrocardia and enlargement of the right heart structures. (*B*) Tracing of *A*. (*C*) Frontal angiocardiogram demonstrating enlargement of the left atrium with the left heart structures in the right hemithorax. (*D*) Tracing of *C*. (Reproduced with permission from the *New York State Journal of Medicine*.)

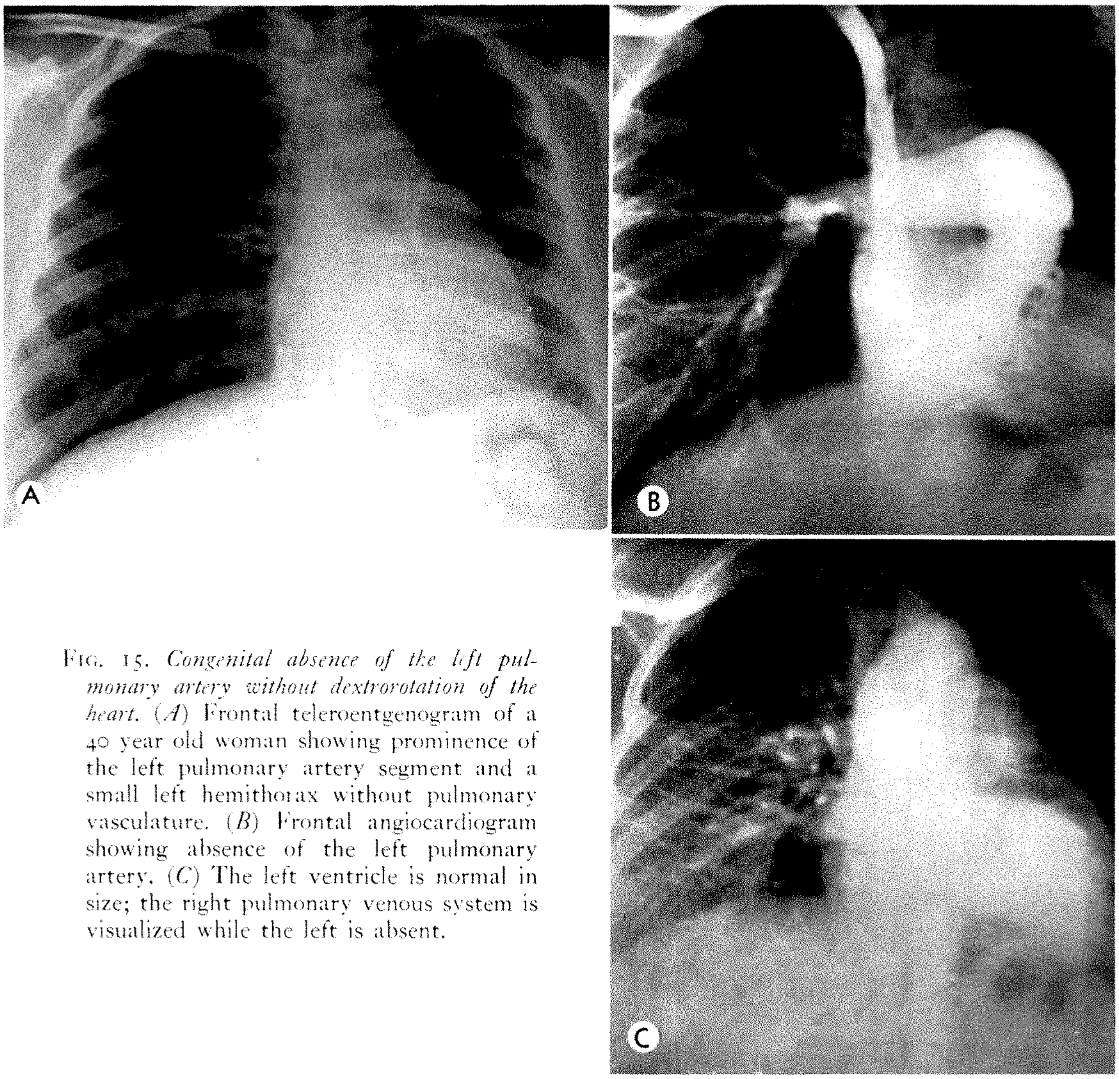

FIG. 15. *Congenital absence of the left pulmonary artery without dextrorotation of the heart.* (*A*) Frontal teleroentgenogram of a 40 year old woman showing prominence of the left pulmonary artery segment and a small left hemithorax without pulmonary vasculature. (*B*) Frontal angiocardiogram showing absence of the left pulmonary artery. (*C*) The left ventricle is normal in size; the right pulmonary venous system is visualized while the left is absent.

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ANGIOCARDIOGRAPHY IN DIAGNOSIS OF CARDIAC TUMORS*

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SIGNIFICANT contributions for diagnosis of cardiac tumors are made by angiocardiography. In atrial myxomas lobulated filling defects often show tendencies to prolapse into their corresponding ventricles during atrial systole and produce signs of valvular stenosis.[7,8,14,17] Differentiation of left atrial myxomas from thrombi is apparently not difficult because huge thrombi owing to rheumatic heart disease are usually associated with left atrial appendage thrombosis, whereas the atrial appendage in cases of myxoma is readily visualized. Intrapericardial tumors cause rotation of the cardiovascular structures within the confines of the pericardium and these can readily be demonstrated by angiocardiography.[16,17] Angiocardiography, by delineating the cardiovascular structures, can establish the presence of pericardial effusions, adjacent mediastinal tumors, and cardiac masses.[18,19] Furthermore, if the cardiovascular structures are intact and without stenoses or occlusions, a benign rather than a malignant lesion may be surmised. In any event, important data, which will help to decide whether exploratory thoracotomy and cardiovascular biopsy are needed, will be obtained by angiocardiography.

METHOD

Intravenous angiocardiography in the erect or supine position with multiple serial roentgenography was performed in all cases.[5,11] Preliminary circulation time determinations with decholin, especially when heart failure or valvular obstruction was suspected, were regularly made in order to estimate the duration of cardiovascular opacification.[15,19] Usually, a second injection for lateral or oblique views was given; in some instances simultaneous biplane studies permitted both the frontal and lateral views with a single injection.

MATERIAL

This material consists of 6 patients with intracavitary lesions (atrial myxomas), 2 of the right atrium (Fig. 1, *A–D*; and 2, *A* and *B*) and 4 of the left atrium (Fig. 3 to 6, inclusive). Four patients had myocardial tumors: a hemangioendothelioma (Fig. 7, *A–F*), a rhabdomyofibroma (Fig. 8, *A* and *B*), tuberous sclerosis (Fig. 9, *A*, *B* and *C*), and an intrapericardial teratocarcinoma (Fig. 10, *A*, *B* and *C*). Only a single patient with a pericardial cyst (Fig. 11, *A–D*) is presented although 11 others have been studied angiocardiographically at this center.[5,18]

ILLUSTRATIVE CASES

*Right Atrial Myxoma.** A 48 year old man with a chief complaint of dyspnea, made worse when lying on the right side or bending, was studied at the Methodist Hospital of Brooklyn. His roentgenograms were made available through the courtesy of Drs. R. Vincent Grieco and Noel F. Bartone (Fig. 1, *A–D*). The frontal conventional roentgenogram showed a normal sized right atrium with prominence of the left

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* This case has recently been reported in detail. (SIGGILLINO, J. J., CRAWLEY, C. J., CLAUSS, R. H., REED, G. E., and TICE, D. A. Myxoma of the right atrium with polycythemia. *Arch. Int. Med.*, 1963, *111*, 178–183).

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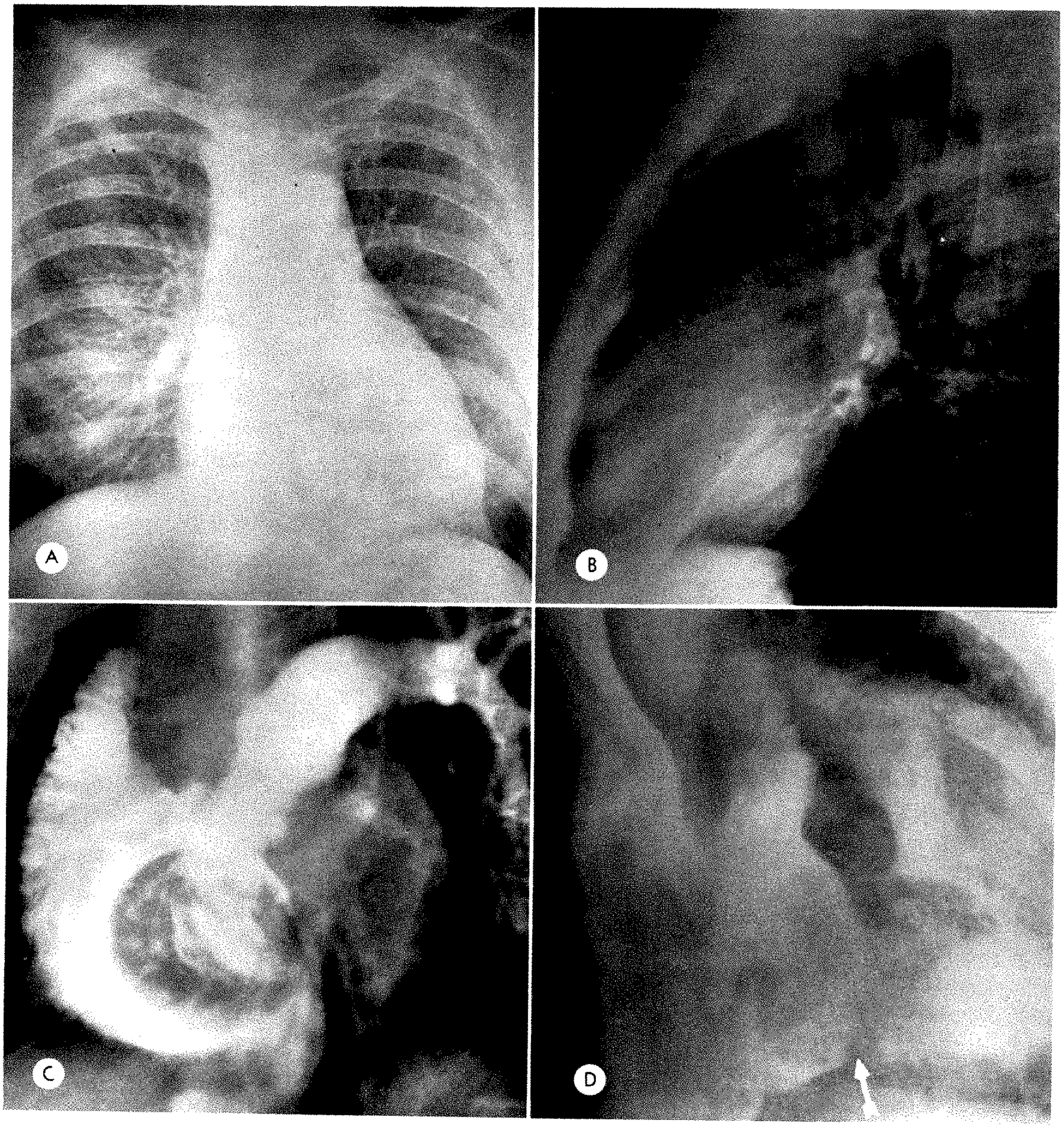

Fig. 1. *Right Atrial Myxoma.* (*A*) Frontal teleroentgenogram of the heart showing prominence of the left cardiac silhouette. (*B*) Lateral teleroentgenogram of the chest demonstrating that there is enlargement of the right ventricle. (*C*) Left oblique angiocardiogram revealing a rounded filling defect in the right atrium. (*D*) Right oblique angiocardiogram showing that the defect is lobulated and extends from the right atrium across the tricuspid valve (arrow) into the right ventricle.

cardiac silhouette (Fig. 1*A*), while the lateral view suggested enlargement of the outflow tract of the right ventricle (Fig. 1*B*). Biplane angiocardiographic studies in oblique positions (the patient was unable to lie supine without discomfort) disclosed a huge lobulated filling defect in the right atrium which extended into the right ventricle (Fig. 1, *C* and *D*).

Another patient, a man aged 51 years with classic findings of tricuspid stenosis, previously reported by Dr. Harold A. Lyons and colleagues,[10] also had a huge right atrial tumor which prolapsed into the right ventricle during atrial systole (Fig. 2, *A* and *B*).

Left Atrial Myxoma. The roentgen studies, made at Triboro Hospital of a 49 year old man

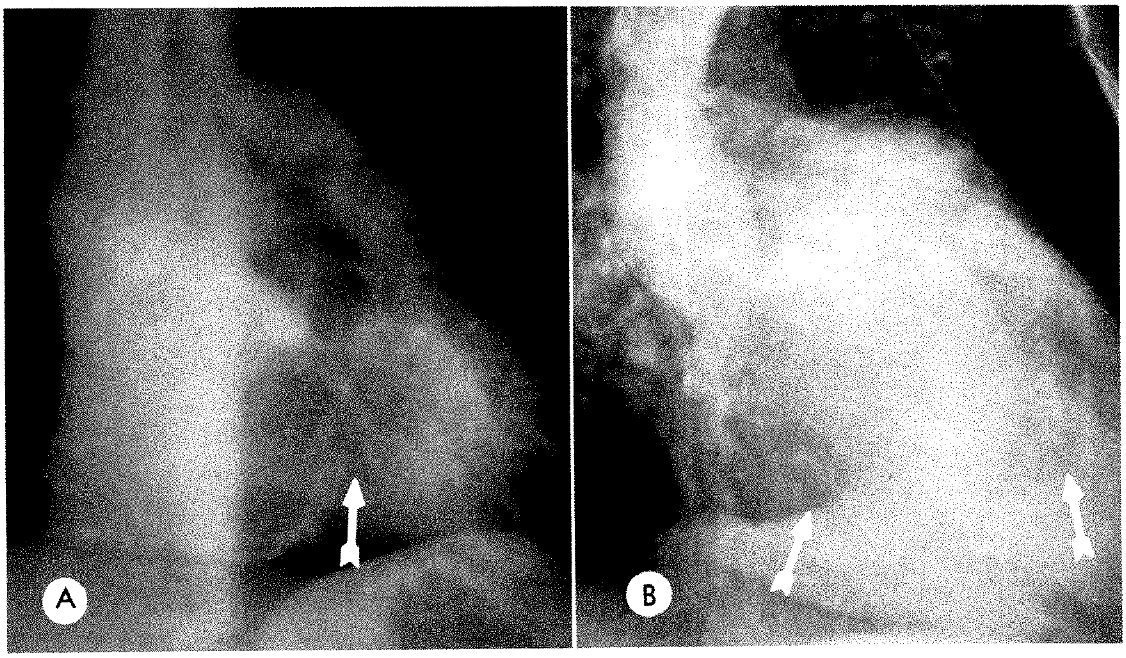

FIG. 2. *Right Atrial Myxoma.* (*A*) Frontal angiocardiogram showing a huge right atrial filling defect adjacent to the tricuspid valve (arrow) and extending into the right ventricle. (*B*) Right oblique angiocardiogram also demonstrating filling defects (arrows) in the right atrium and ventricle.

with left atrial myxoma with symptoms and physical signs of mitral stenosis are shown in Figure 3, *A–D*. The conventional frontal roentgenogram shows prominence of the right border of the left atrium (Fig. 3*A*). Angiocardiograms disclosed a huge filling defect which traveled from the atrium to the left ventricle during atrial systole (Fig. 3, *B* and *C*). Open-heart operation permitted removal of the myxoma. A roentgenogram following the operation was normal (Fig. 3*D*). Representative angiocardiograms of 3 patients, 2 with physical signs of mitral stenosis and previously studied at The New York Hospital, are shown in Figures 4 to 6, inclusive.[7,11] All had left atrial filling defects; however, the left atrial appendage in each case was well opacified.

*Cardiac Hemangioendothelioma.** In 1952, this patient at the age of 2 years had pneumonia followed by ascites, hepatomegaly, and a gallop rhythm. The heart was enlarged and an electrocardiogram suggested pericarditis. She improved, but when almost 3 years old developed dyspnea, cough, and fatigue. Thoracotomy yielded 200 cc. of clear fluid from the pericardial sac, cultures of which were negative. Partial pericardiectomy was done. The biopsy of the pericardium showed "collagenous thickening." She gradually improved and achieved normal growth and activity. At 10 years of age, she was a tall, thin girl who appeared well except for a bulge of the left precordium. The heart was enlarged to the left with dullness at the anterior axillary line. The rhythm was regular, the heart sounds were normal, and no murmurs were heard. The lungs were clear. There was no venous distention and the liver was not enlarged. Roentgenoscopy and roentgenography revealed a large left ventricle which showed almost no pulsations (Fig. 7, *A* and *B*). The electrocardiogram showed right axis deviation, sharply inverted T waves in leads, 1, 2, $V_{3,4,5}$ and 6; Rr^1 pattern in leads V_{3R}, V_1 and 3, with deep (30 mm.) V_5 and V_6. Roentgenoscopy had suggested the possibility of a cardiac tumor· this was confirmed by angiocardiography (Fig. 7, *C*, *D* and *E*).

Rhabdomyofibroma of the Heart. An 18 month old infant had been treated at the age of 6 weeks for congestive heart failure. He encountered no difficulties in growth, development, or activity, but at 16½ months was seen because of cardiac enlargement detected during

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* Captain Joseph J. Timmes, (MC) USN, U. S. Naval Hospital, St. Albans, New York, kindly gave permission to include this case.

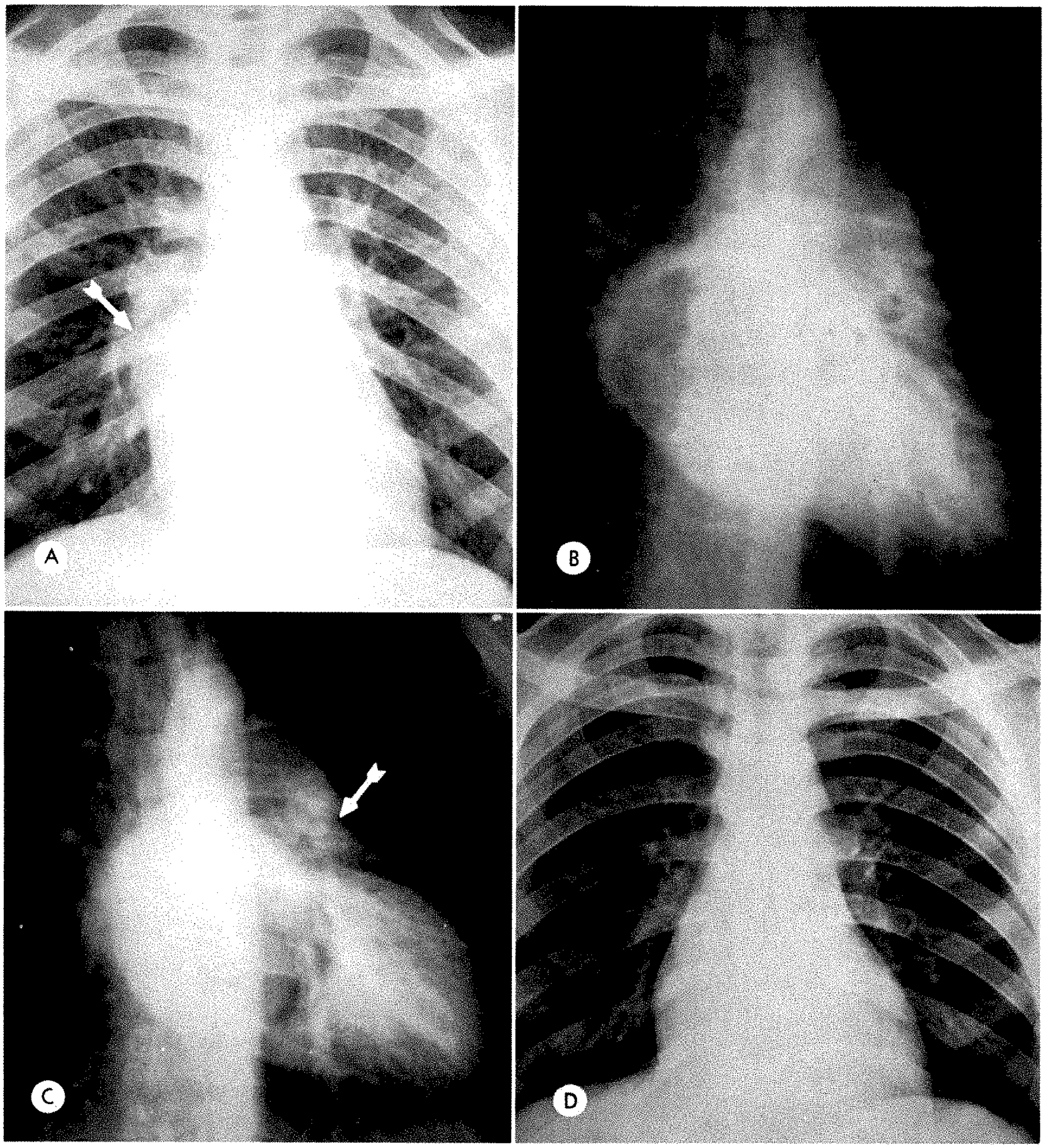

Fig. 3. *Left Atrial Myxoma.* (*A*) Frontal teleroentgenogram of the chest showing an enlarged right border of the left atrium (arrow). (*B*) Frontal angiocardiogram during left atrial systole showing a huge filling defect along the right border of the left atrium. (*C*) During left atrial systole the filling defect extends into the left ventricle. Note the opacified left atrial appendage (arrow). (*D*) Postoperative frontal teleroentgenogram showing a normal cardiac silhouette.

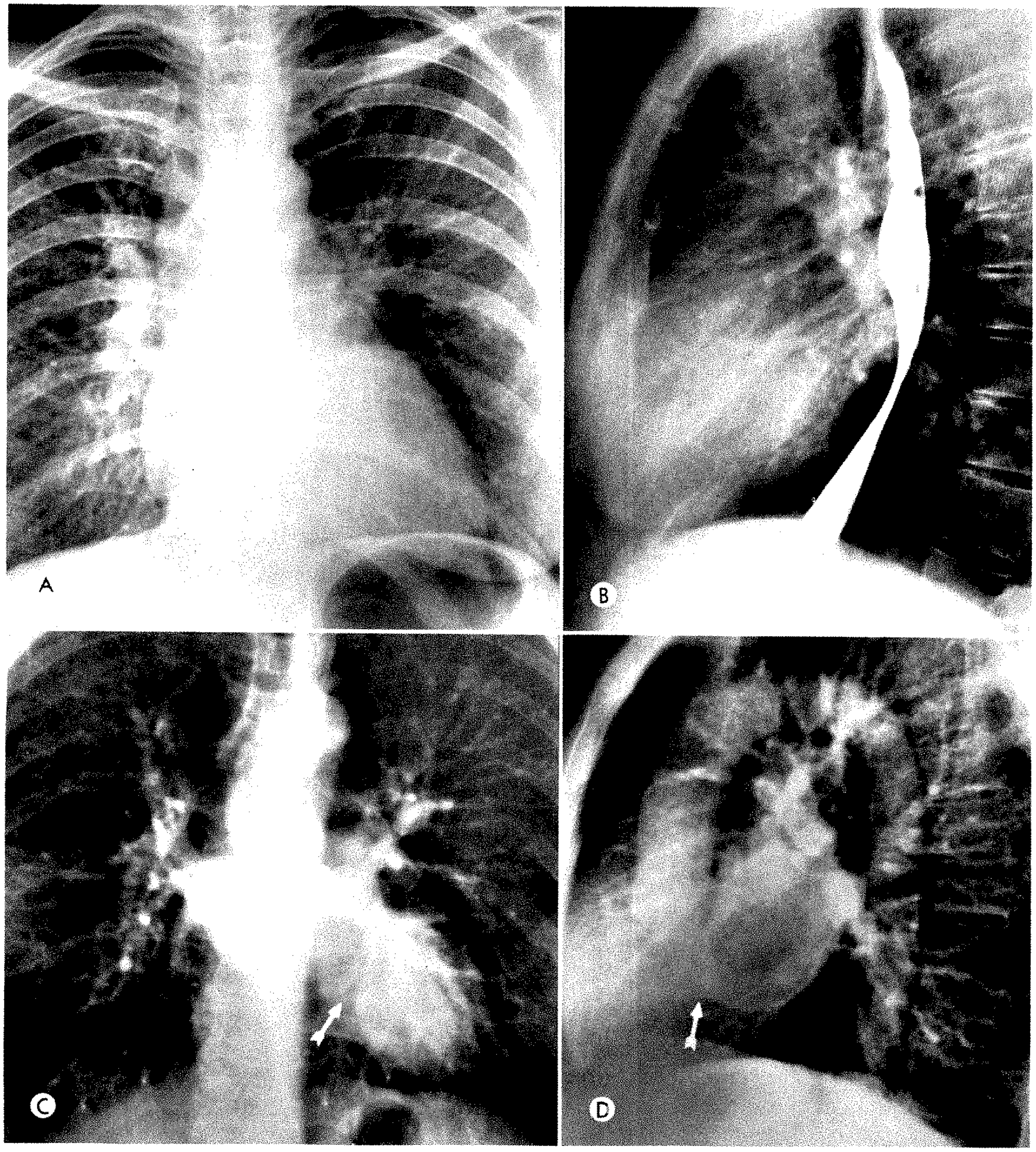

Fig. 4. *Left Atrial Myxoma.* (*A*) Frontal teleroentgenogram of the chest showing enlargement of the heart, pulmonary artery, and left atrium. (*B*) Lateral esophagram with indentation owing to left atrial enlargement. (*C*) Frontal angiocardiogram revealing a filling defect adjacent to the mitral valve (arrow). Note the opacified left atrial appendage. (*D*) Lateral angiocardiogram showing a huge filling defect occupying most of the lower portion of the left atrium. Arrow points to the mitral valve. (Reproduced with permission of the publisher.[14])

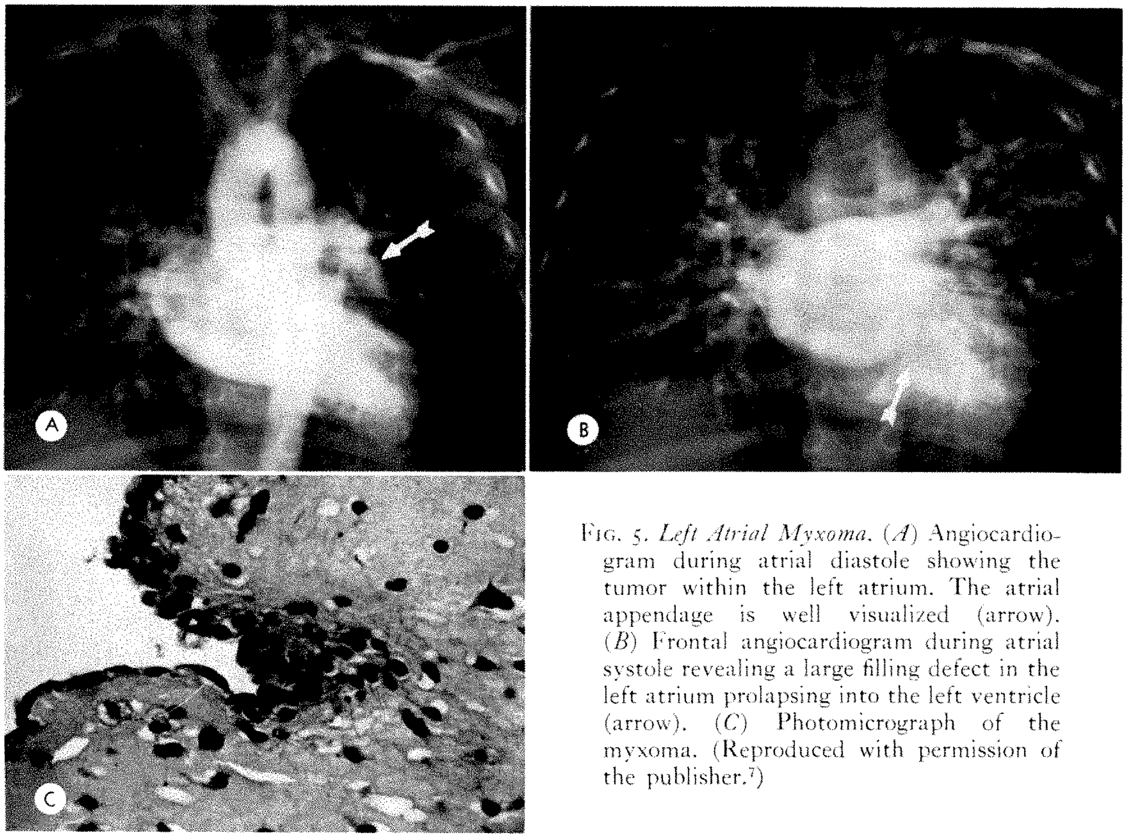

Fig. 5. *Left Atrial Myxoma.* (*A*) Angiocardiogram during atrial diastole showing the tumor within the left atrium. The atrial appendage is well visualized (arrow). (*B*) Frontal angiocardiogram during atrial systole revealing a large filling defect in the left atrium prolapsing into the left ventricle (arrow). (*C*) Photomicrograph of the myxoma. (Reproduced with permission of the publisher.[7])

hospitalization for severe tonsillitis. A considerable bulge of the left lateral chest wall was noted. Cardiac dullness extended almost to the left anterior axillary line. The rhythm was regular and the sounds were normal. The radial and femoral pulses were also normal. Over the left precordium a soft, short, slightly blowing systolic murmur and a short mid-diastolic murmur were heard. Roentgenoscopy revealed the left ventricle to be large but no pulsations were detected. The roentgenograms of the chest showed enlargement of the left ventricle (Fig. 8*A*). A review of the roentgenograms made at the age of 6 weeks also disclosed an abnormal shadow in the region of the left ventricle. Angiocardiography bore out the clinical diagnosis of a cardiac tumor. Surgery was unsuccessful because the tumor involved an extensive area of the ventricular wall. Microscopic examination led to the diagnosis of rhabdomyofibroma (Fig. 8*B*).

Cardiac Enlargement and Pericardial Effusion in Tuberous Sclerosis. Myoclonic seizures, which began at the age of 7 months and were inadequately controlled by phenobarbital, led to the referral of this infant to The New York Hospital at the age of 14 months. She was a fairly well-developed, slightly thin girl who presented no abnormalities on physical examination except for an apical systolic murmur. The seizures were subsequently well controlled with larger dosage of phenobarbital. At 27 months of age, apical systolic and diastolic murmurs and cardiac enlargement were noted (Fig. 9*A*). Adenoma sebaceum of the face became more conspicuous. An intravenous pyelogram demonstrated a filling defect in the mid-portion of the left kidney. The optic fundi, at first unremarkable, later showed plaques characteristic of tuberous sclerosis. Cardiac catheterization supported the diagnosis of mitral insufficiency and angiocardiograms demonstrated a large left atrium, ventricle, and pericardial effusion (Fig. 9, *B* and *C*). It appears that the cardiac lesion in this patient consists of rhabdomyomata as a part of the general process of tuberous sclerosis.[6]

Intrapericardial Teratocarcinoma. At 3 years of age, this patient was first admitted to another hospital with signs of superior mediastinal obstruction. A chest roentgenogram disclosed an

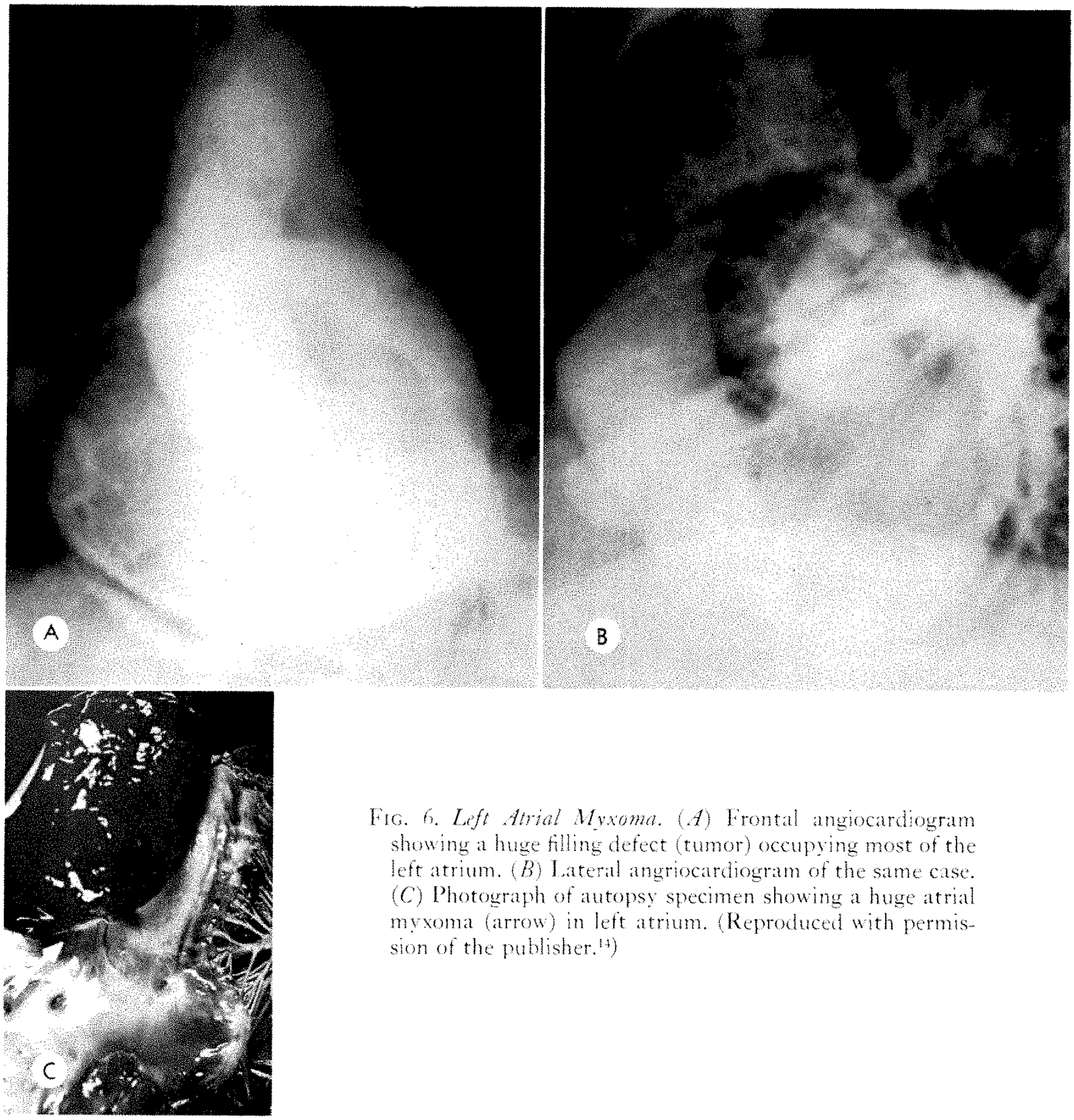

FIG. 6. *Left Atrial Myxoma.* (*A*) Frontal angiocardiogram showing a huge filling defect (tumor) occupying most of the left atrium. (*B*) Lateral angriocardiogram of the same case. (*C*) Photograph of autopsy specimen showing a huge atrial myxoma (arrow) in left atrium. (Reproduced with permission of the publisher.[14])

anterior mediastinal mass. A clinical diagnosis of thymoma was followed by roentgen irradiation and nitrogen mustard therapy. At first, there was clinical improvement but without regression of the cardiac mass. She was transferred to another hospital where a biopsy was obtained through a small thoracotomy incision in the fourth left interspace in the mid-clavicular line. The available tissue was considered part of a bronchiogenic cyst. After examination in The Pediatric Cardiac Clinic, she was admitted into The New York Hospital for further study and treatment. There were no abnormal cardiac findings but the neck veins were distended bilaterally. Roentgenoscopy and roentgenography of the chest disclosed an anterior mediastinal mass and a large nonpulsatile shadow in the region of the right atrium (Fig. 10*A*). The angiocardiograms demonstrated pericardial effusion, a large nonopacified intrapericardial mass, and complete obstruction of the right subclavian vein (Fig. 10*B*).[16] An attempt at surgical resection was abandoned since the tumor had extensively invaded the pericardial sac and the right atrial and ventricular walls. The sections of the biopsy were interpreted as showing teratocarcinoma (Fig. 10*C*). She failed to respond to intensive roentgen ir-

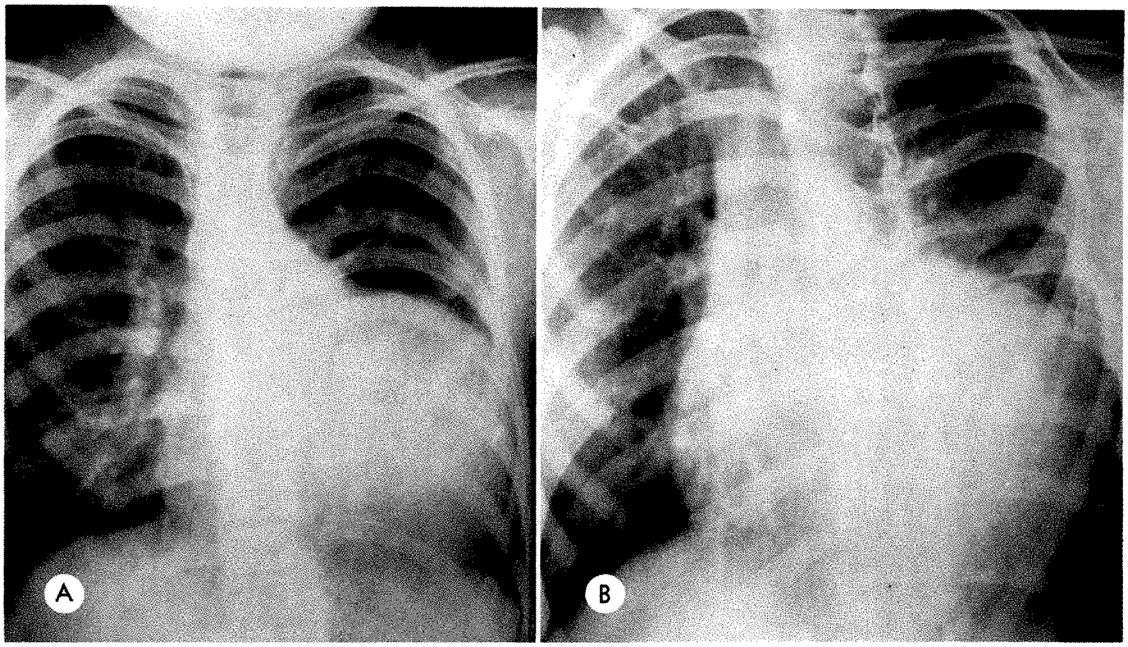

Fig. 7. *Hemangioendothelioma of the Heart.* (*A*) Frontal teleroentgenogram revealing marked enlargement of the heart, especially the left ventricle. (*B*) Left anterior oblique roentgenogram also showing enlargement of the right ventricle.

radiation and chemotherapy, and died at the age of 4 years.

Pericardial Cyst. A 4 year old asymptomatic boy was noted by his pediatrician to have an unusual cardiac contour on routine roentgenoscopy of the chest. Roentgenograms of the chest showed a bulge of the left cardiac border (Fig. 11*A*). Physical examination was unremarkable except for a systolic murmur (Grade 2) heard over the entire precordium, loudest at the apex but not transmitted, which was considered to be functional. The electrocardiogram showed questionable left ventricular hypertrophy. Angiocardiograms revealed normal cardiac chambers and great vessels. A mass, lateral and anterior to the left ventricle, did not fill with contrast material (Fig. 11*B*). The smooth contour of the opacified left ventricle, however, did not suggest a tumor of the wall of the ventricle. A pericardial cyst was, therefore, considered the most likely diagnosis.

Surgery was performed through the left chest. A pericardial cyst which had a direct communication with the pericardial sac was found and excised without incident. The postoperative course was unremarkable. Pathologic examination of the cyst after removal revealed it to be thin-walled with a smooth lining which when flattened out measured 6.5 by 3 cm. Microscopically, the wall contained dense fibrous connective tissue and vascular elements. The cyst lining was composed of a single layer of mesothelial cells (Fig. 11*C*). The normal postoperative roentgen study of the thorax is shown in Figure 11*D*.

DISCUSSION

Angiocardiography by delineating the cardiovascular stuctures is the definitive method for the diagnosis of atrial myxomas. Recent reports and reviews[1–4,9,12,13,21] emphasize this. Intracavitary cardiac tumors produce filling defects which are readily demonstrated on angiocardiograms. Both right and left atrial myxomas are usually lobulated, attached to the atrial wall, and have a tendency to traverse their respective valves and produce murmurs of valvular disease when they prolapse into the ventricle, especially during atrial systole (Fig. 1, *C* and *D*; 2, *A* and *B*; 3, *B* and *C*; 4, *C* and *D*; 5*A*; and 6, *A* and *B*). Differentiation from a huge left atrial thrombus owing to rheumatic mitral ste-

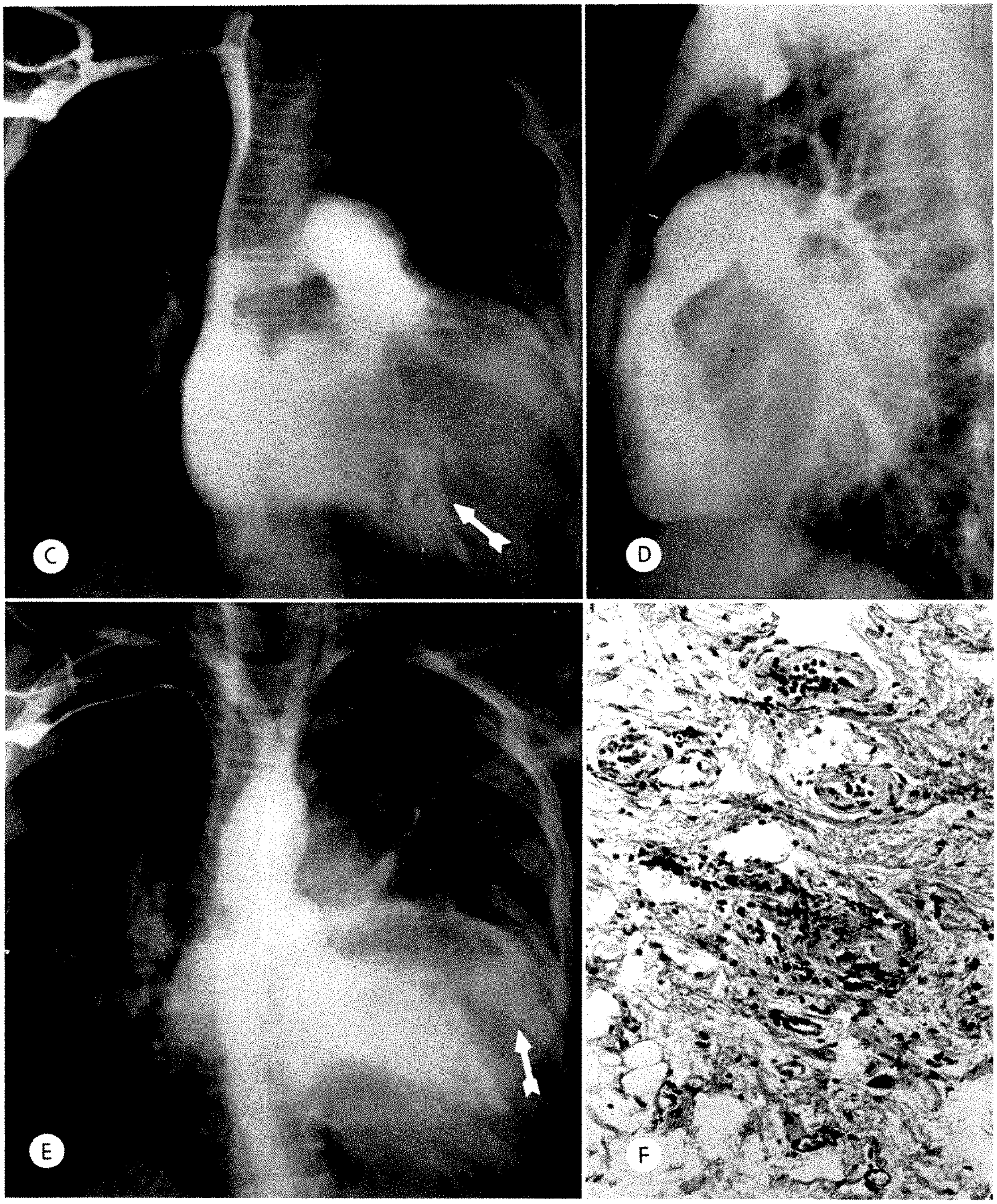

Fig. 7. (*C*) Frontal angiocardiogram demonstrating the enlarged right ventricle with trabeculae (arrow). (*D*) Lateral angiocardiogram showing that the enlargement of the heart is chiefly of the left ventricle. (*E*) Frontal angiocardiogram demonstrating the huge left ventricular wall containing lakes of contrast material (arrow). (*F*) Photomicrograph of biopsy material showing hemangioendothelioma.

nosis is of academic interest, since removal of the mass is indicated in both instances. All patients with left atrial myxomas in the present series had patent left atrial appendages angiocardiographically, whereas the patient with the huge thrombus (Fig. 12, *A* and *B*) also had thrombosis of the left atrial appendage (Fig. 12*B*).

Mural tumors of the heart should be suspected when angiocardiograms show an isolated and unusually thickened cardiac wall of obscure etiology (Fig. 7*E*). In such instances exploratory operation and myocardial biopsy are indicated and will establish the diagnosis (Fig. 7*F*).

Pericardial cysts are usually adjacent to some portion of the pericardium. Angiocardiography may indicate this, but cannot differentiate them from adjacent mediastinal tumors. Accordingly, thoracotomy is necessary for definitive diagnosis and treatment. Cystic intrapericardial masses (bronchiogenic cysts) and teratocarcinomas have a tendency to rotate the cardiovascular structures within the confines of the pericardium. Accordingly, angiocardiography may be expected to reveal the cardiovascular structures dislocated into either the right or left oblique position by the huge nonopacified intrapericardial mass.[16] In the case of the teratocarcinomatous intrapericardial tumor, invasive features such as pericardial effusion, occlusion of the great veins, and stenoses of the superior vena cava and pulmonary conus were also revealed (Fig. 10*B*).[16]

Pericardial effusions are easily demonstrated on angiocardiograms (Fig. 9, *B* and *C;* and 10*B*).[18] Usually, there is a so-called soft tissue density which surrounds the opacified cardiac chambers when they are visualized in the frontal view. This can be confirmed by pericardiocentesis; study of the fluid may establish the etiology of the effusion. In 2 patients with intrapericardial lipomata, these could not be distinguished from pericardial effusions. One patient also had an anterior mediastinal lipoma which simulated a dermoid cyst.

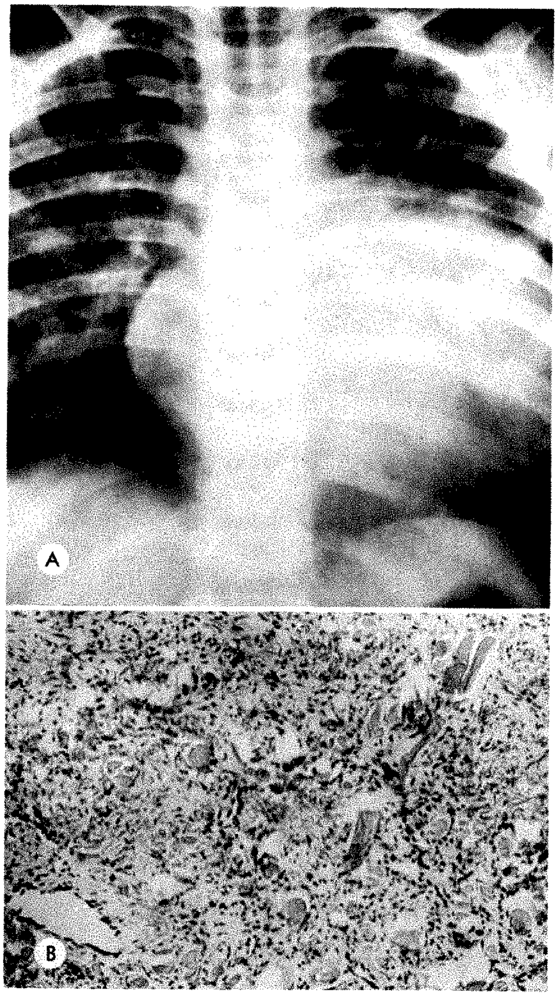

Fig. 8. *Rhabdomyofibroma of the Heart.* (*A*) Frontal roentgenogram of the chest showing a huge heart. (*B*) Photomicrograph of the tumor showing rhabdomyofibroma.

SUMMARY AND CONCLUSIONS

Angiocardiography is indicated whenever there are massive cardiac shadows or unusual heart murmurs, especially the signs of either tricuspid or mitral stenosis. With contrast studies cardiac dilatation can readily be differentiated from pericardial effusion. Intrapericardial tumor should be suspected when the cardiac chambers are rotated within the confines of the pericardium. Mediastinal tumors or pericardial cysts adjacent to the heart can usually be distinguished from intrapericardial and cardiac tumors by angiocardi-

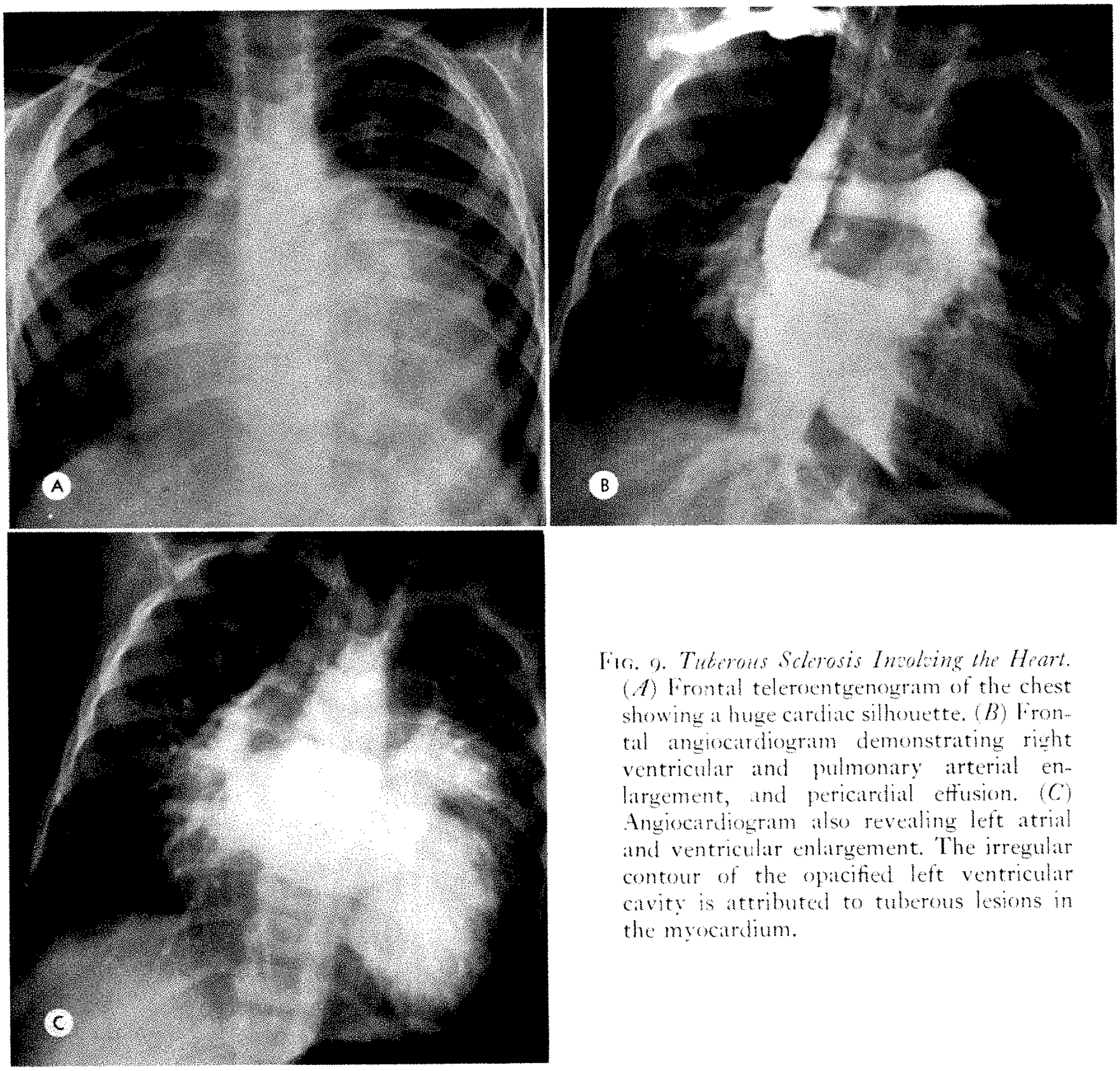

FIG. 9. *Tuberous Sclerosis Involving the Heart.* (*A*) Frontal teleroentgenogram of the chest showing a huge cardiac silhouette. (*B*) Frontal angiocardiogram demonstrating right ventricular and pulmonary arterial enlargement, and pericardial effusion. (*C*) Angiocardiogram also revealing left atrial and ventricular enlargement. The irregular contour of the opacified left ventricular cavity is attributed to tuberous lesions in the myocardium.

ography. Finally, intracavitary cardiac tumors (myxomas) which frequently cause murmurs of valvular stenosis can be readily recognized because they have lobulated filling defects which partially occlude the tricuspid or mitral valves during atrial systole. Since open-heart surgery and removal of the myxoma is curative, the angiocardiographic diagnosis is essential.

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ADDENDUM

Since this paper was prepared for publication, a 38 year old woman with the superior vena cava syndrome (headache, swelling of the face, neck and chest, and venous engorgement of the thorax) was studied on Dec. 17, 1962. She also illustrates the value of angiocardiography in the diagnosis of cardiac tumor. Conventional roentgenography of the chest had revealed widening of the middle superior mediastinum (Fig. 13*A*). Angiocardiography showed both subclavian and innomi-

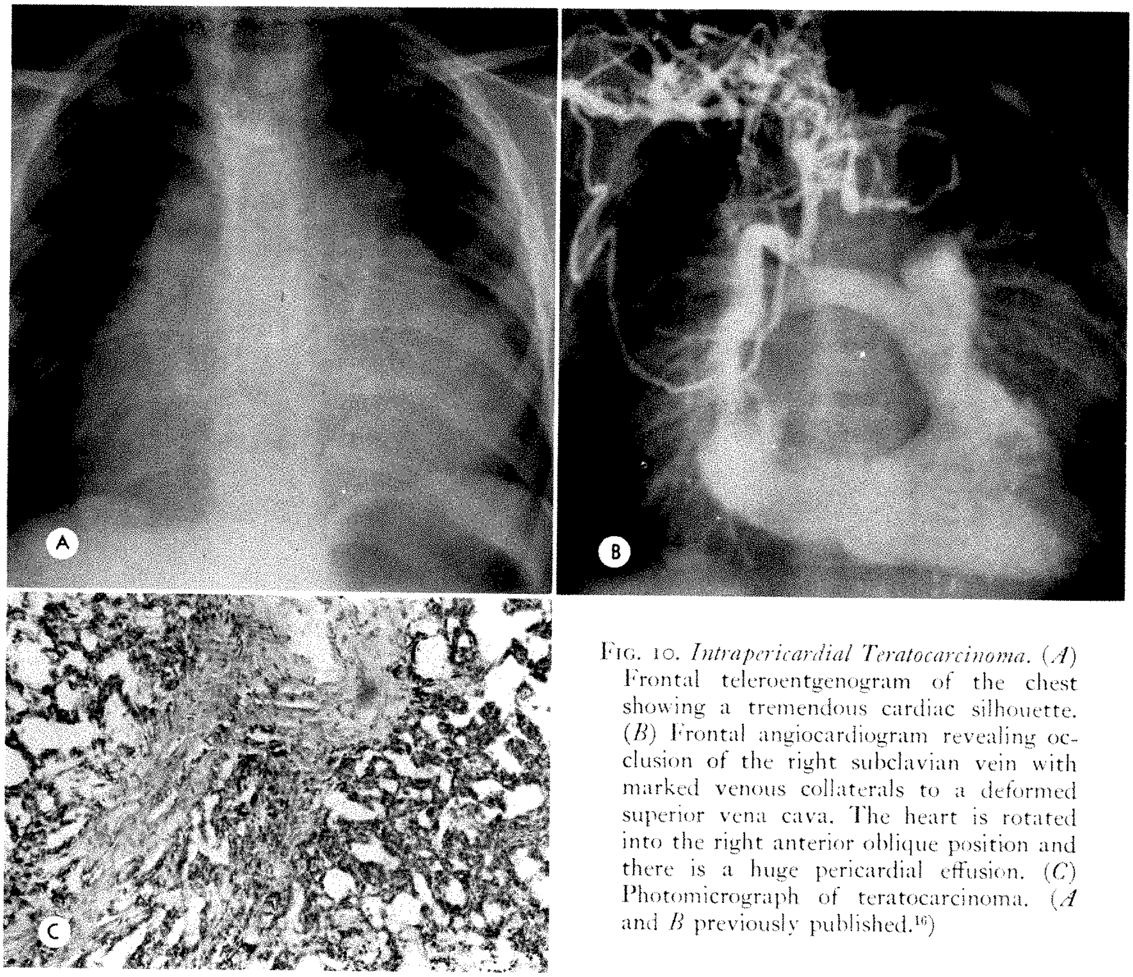

FIG. 10. *Intrapericardial Teratocarcinoma.* (*A*) Frontal teleroentgenogram of the chest showing a tremendous cardiac silhouette. (*B*) Frontal angiocardiogram revealing occlusion of the right subclavian vein with marked venous collaterals to a deformed superior vena cava. The heart is rotated into the right anterior oblique position and there is a huge pericardial effusion. (*C*) Photomicrograph of teratocarcinoma. (*A* and *B* previously published.[16])

nate veins to be intact (Fig. 13, *B* and *C*). The superior vena cava was occluded and blood flow was through a hugely dilated azygos system (Fig. 13, *B* and *C*). Serial roentgenography disclosed only filling of the inferior portion of the right atrium via blood flow from the inferior vena cava; the upper half of the atrium contained a filling defect (Fig. 13*D*).

Operation on January 18, 1963, verified the occlusion of the upper portion of the right atrium and superior vena cava by tumor. Cardiac arrest occurred during operation and even though a heart-lung machine was in use, it was not possible to revive the patient. Histologic study of the specimen showed a very bizarre malignant tumor—undifferentiated spindle cell sarcoma.

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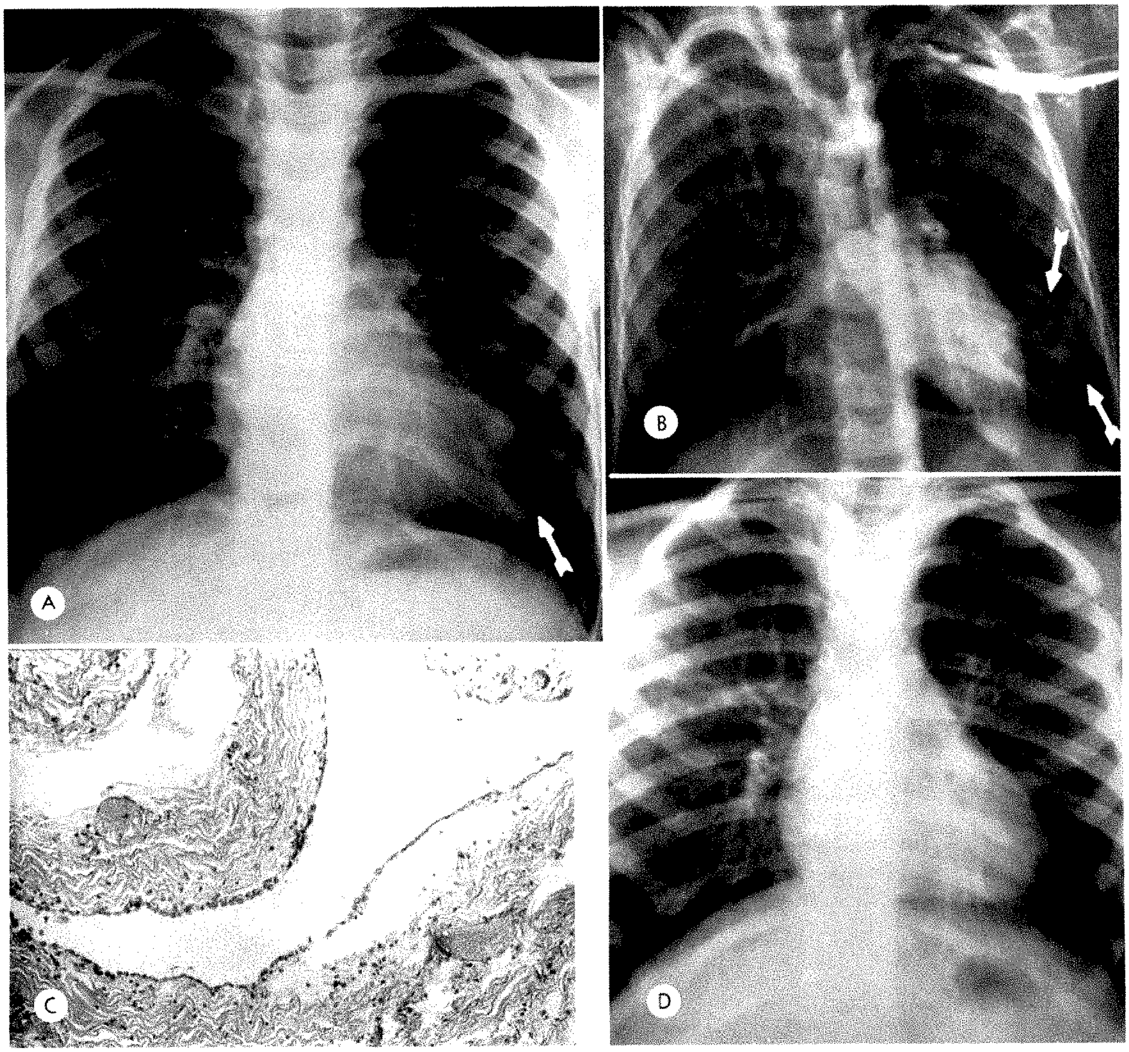

FIG. 11. *Pericardial Cyst.* (*A*) Frontal teleroentgenogram of the chest showing prominence of the left ventricular contour (arrow). (*B*) Frontal angiocardiogram showing the left atrium and ventricle to be normal in size and contour. A nonopacified extracardiac mass (arrows) proved to be a pericardial cyst at operation. (*C*) Photomicrograph showing the classic features of a pericardial cyst. (*D*) Postoperative roentgenogram showing the normal cardiac silhouette.

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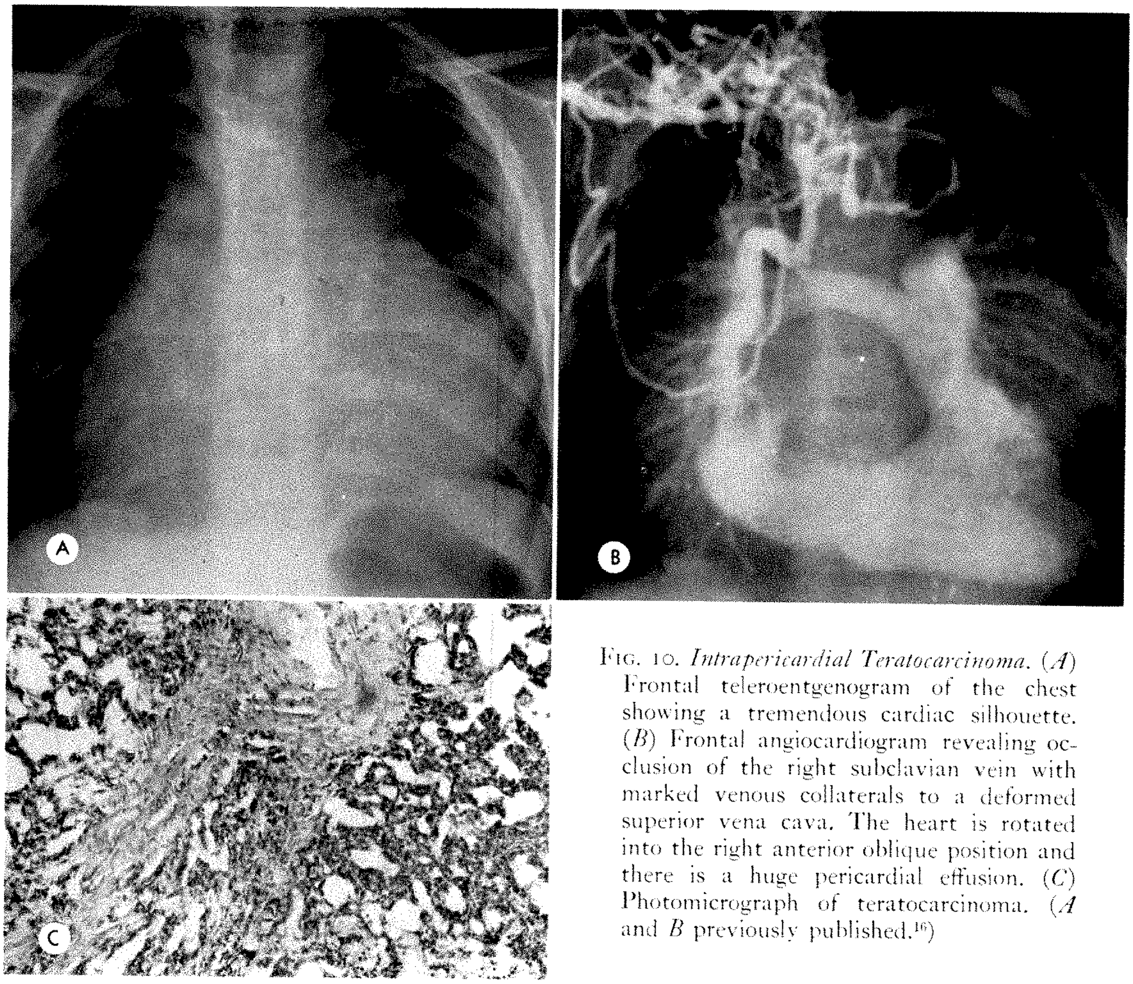

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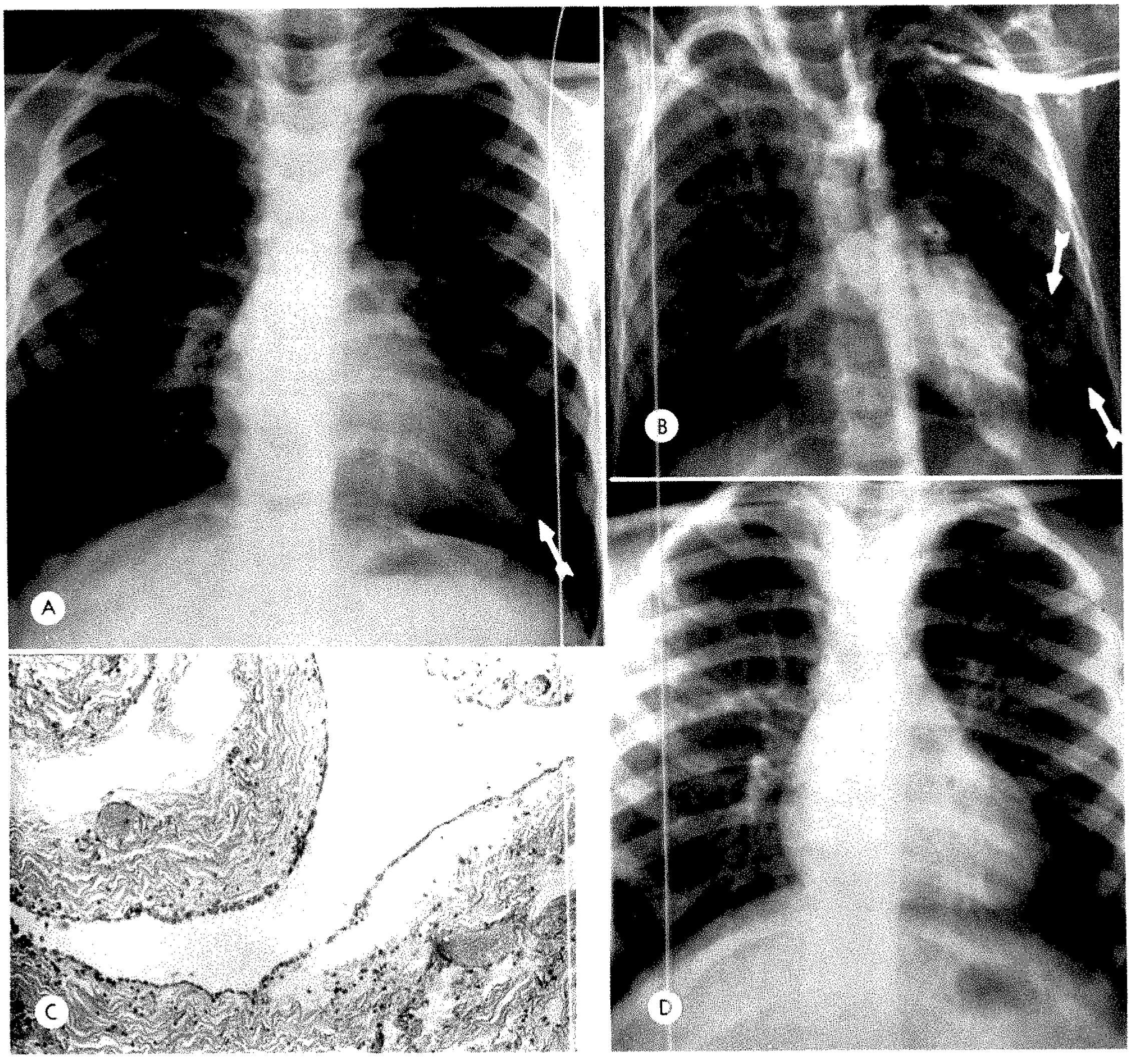

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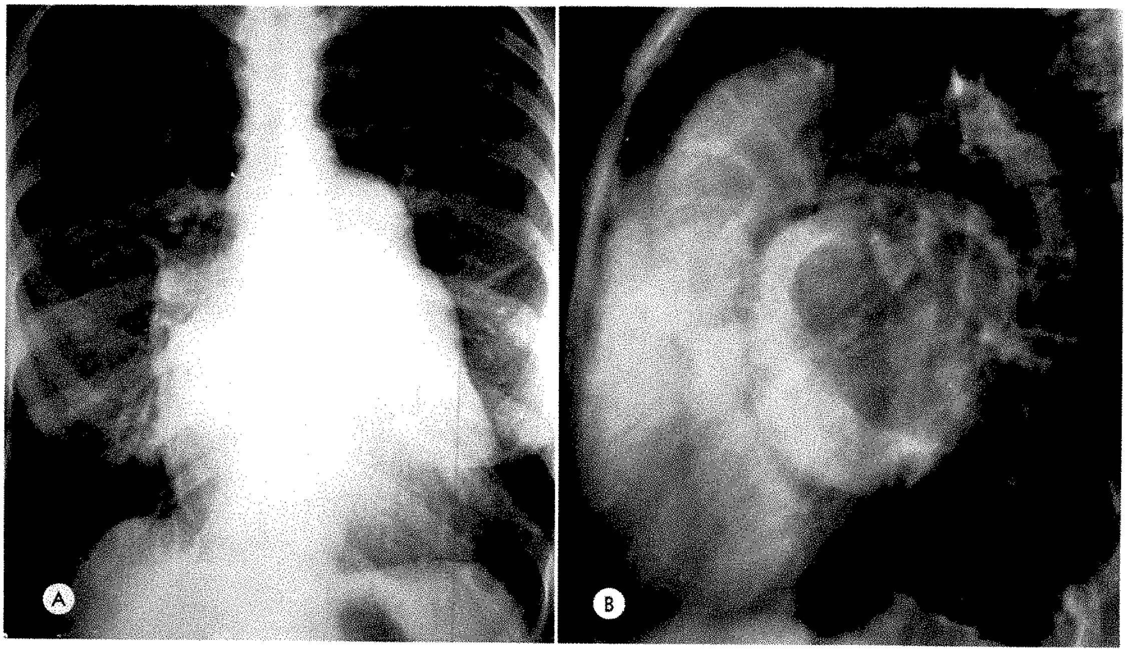

Fig. 12. *Huge Left Atrial Thrombus in Rheumatic Mitral Stenosis.* A 41 year old woman with classic signs of mitral stenosis had severe dyspnea, cyanosis, and congestive heart failure. (*A*) Frontal teleroentgenogram of the chest showing enlargement of the heart, especially of the left atrium, pulmonary artery and branches. (*B*) Lateral angiocardiogram revealing a huge irregular filling defect; the left atrial appendage was not visualized. At open-heart operation a huge left atrial thrombus was removed. Marked improvement followed.

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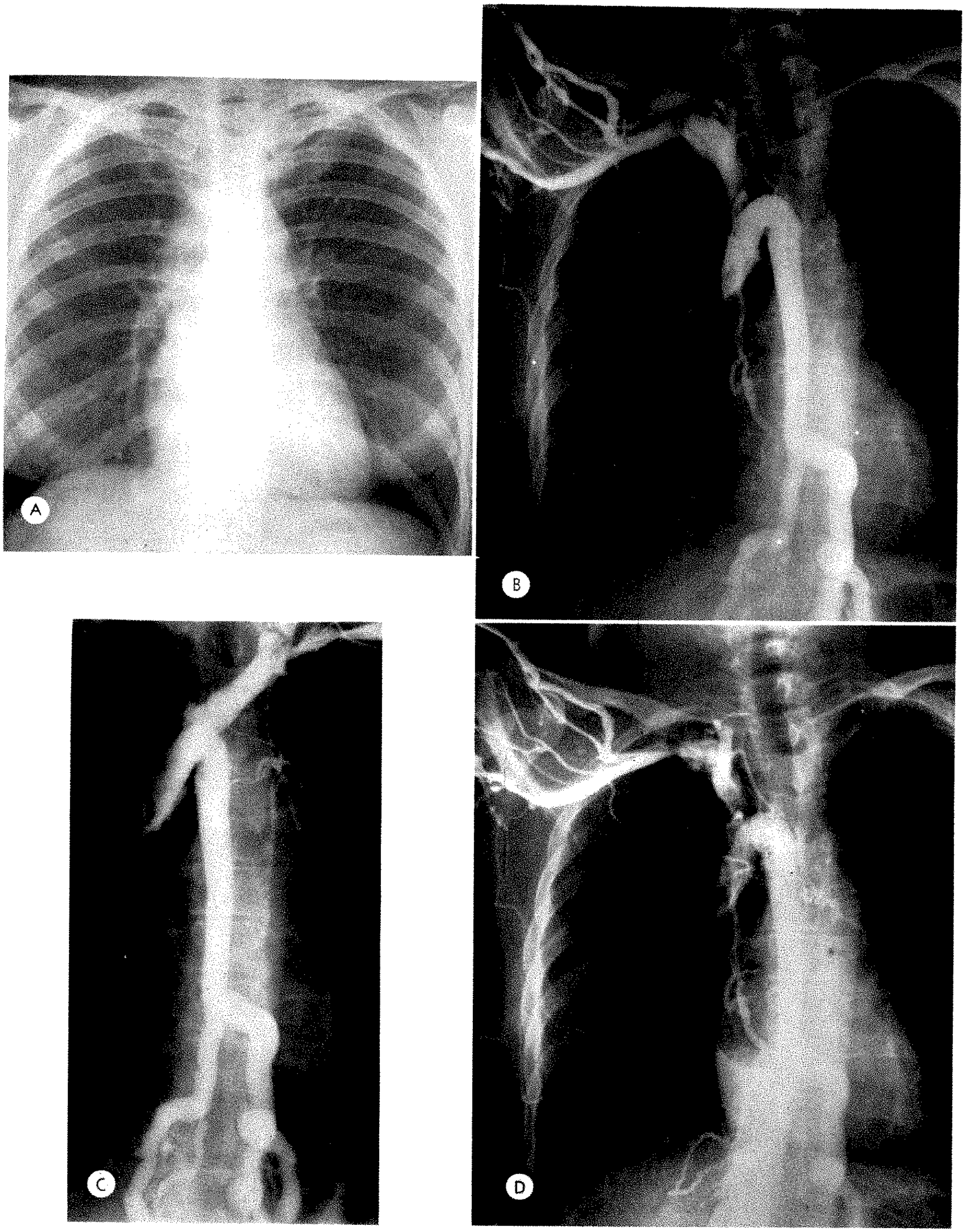

Fig. 13. *Malignant Tumor of the Right Atrium Occluding Superior Vena Cava.* (*A*) Conventional frontal teleroentgenogram of the chest showing widening of the right superior mediastinum. (*B*) Frontal angiocardiogram showing the right subclavian and innominate veins with opacification of a hugely dilated azygos system. (*C*) Angiocardiogram following injection of left arm vein and demonstrating that the left subclavian and innominate veins are intact. (*D*) Later angiocardiogram in the series revealing blood flow in retrograde fashion from the azygos system into the inferior vena cava. Note that there is a huge filling defect in the upper portion of the right atrium.

MULTIPLE MYCOTIC PULMONARY ARTERY ANEURYSMS*

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TWO cases of multiple mycotic pulmonary artery aneurysms were diagnosed recently at the University of Illinois Research and Educational Hospitals. The pathogenesis differed but strikingly similar findings were noted on plain roentgenograms, laminagrams and angiograms.

REPORT OF CASES

CASE I. This 20 year old female, with heart murmur detected at the age of 5 years, had no cyanosis. When she was admitted to Research and Educational Hospitals, her symptoms were fever and hemoptysis which were present for a period of 3 years. Subacute bacterial endocarditis was diagnosed elsewhere and she had been treated intermittently with penicillin. During the month before admission she developed easy fatigability, dyspnea, fever up to 104°F. and more pronounced hemoptysis. No information could be obtained regarding her chest roentgenograms prior to admission. The patient appeared fairly healthy despite the long standing history of fever and weight loss. She had no orthopnea, edema or cyanosis. The pulse rate was 90, and the blood pressure 120/55. A systolic and diastolic thrill was felt in the second left intercostal space. On auscultation S1 was loud and maximum at the apex, S2 was normally split and the pulmonic component of S2 was loud. There was a Grade IV-VI systolic and diastolic murmur over the left intercostal spaces, radiating toward the left shoulder. No spleen or liver enlargement was noted.

A vectorcardiogram revealed right ventricular and right atrial enlargement.

Chest roentgenograms (Fig. 1, *A* and *B*) showed a large pulmonary artery, and multiple round and fusiform masses near the hili and also in the periphery of the lungs. Laminagrams in the frontal and lateral positions (Fig. 2, *A* and *B*) showed the distribution of the masses, but differentiating tumors from inflammatory foci or vascular lesions was not possible.

After the pulmonary function test showed a decrease in ventilatory ability without airway obstruction and since pO_2 rose to about 99 per cent with inhalation of 100 per cent oxygen, it was concluded that there was no evidence of arteriovenous shunt.

Multiple blood cultures yielded alpha hemolytic streptococci which confirmed the diagnosis of subacute bacterial endocarditis.

Cardiac catheterization was unsuccessful but an aortic angiogram demonstrated a small patent ductus arteriosus. In order to clarify the character of the multiple masses, a venous angiogram was made (Fig. 3). The catheter was placed in the pulmonary artery and contrast material was injected. With visualization of the pulmonary artery and its branches multiple round and fusiform areas opacified. They corresponded exactly to the masses seen on the plain chest roentgenograms and laminagrams. The aneurysms remained filled with contrast material during the venous phase, probably due to the lack of elasticity of the dilated segments of the arteries. No arteriovenous shunt was demonstrated.

The patent ductus arteriosus was repaired and during the thoracotomy multiple mycotic aneurysms of the pulmonary artery were palpated. No biopsy was done.

CASE II. A 47 year old taxi driver with a history of night sweats, malaise and frankly purulent sputum of 1 year's duration prior to the admission to the Research and Educational Hospitals was treated with injections by his local physician for "bronchitis" and he improved subjectively. Three months later he noted the onset of exertional dyspnea with continuous malaise. A chest roentgenogram made with a mobile unit was reported as normal. However, more injections were given for "pneumonitis" with lessening of the night sweats. Three months prior to admission he experienced hemoptysis and a chest roentgenogram showed "coin lesions."

The patient was well nourished, was in no distress and showed no cyanosis. The blood pressure was 105/70, pulse 88, and respiration

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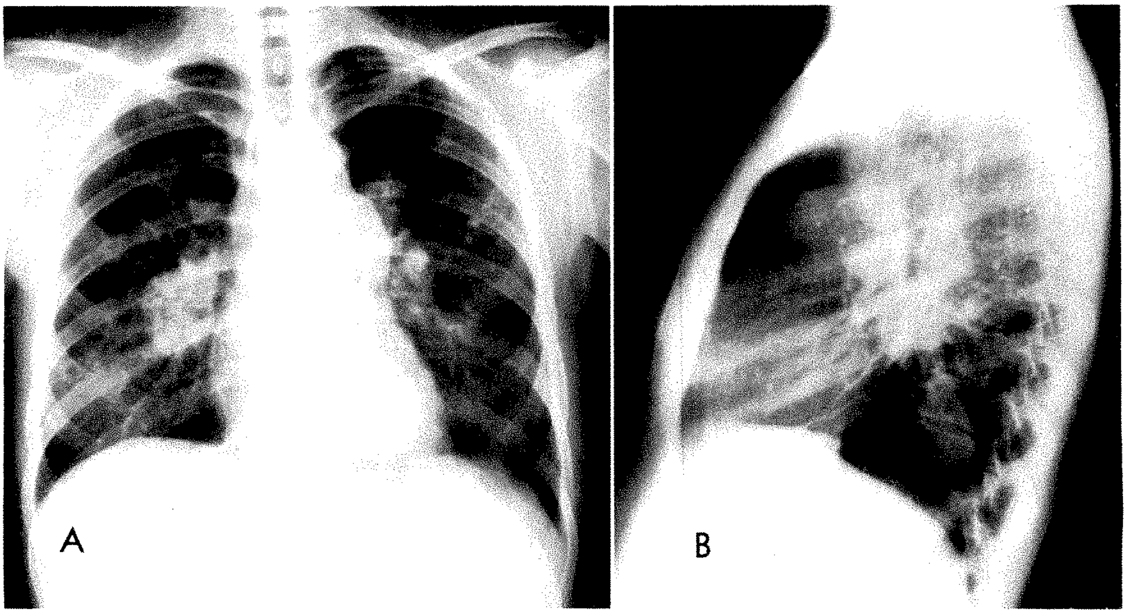

Fig. 1. Case 1. (*A*) Posteroanterior and (*B*) lateral chest roentgenograms of a patient with patent ductus arteriosus and subacute bacterial endocarditis. The large pulmonary artery is consistent with the congenital defect. Multiple masses are seen around the hili, the most distant of which is in the left lower lobe (seen behind the heart shadow on *A*).

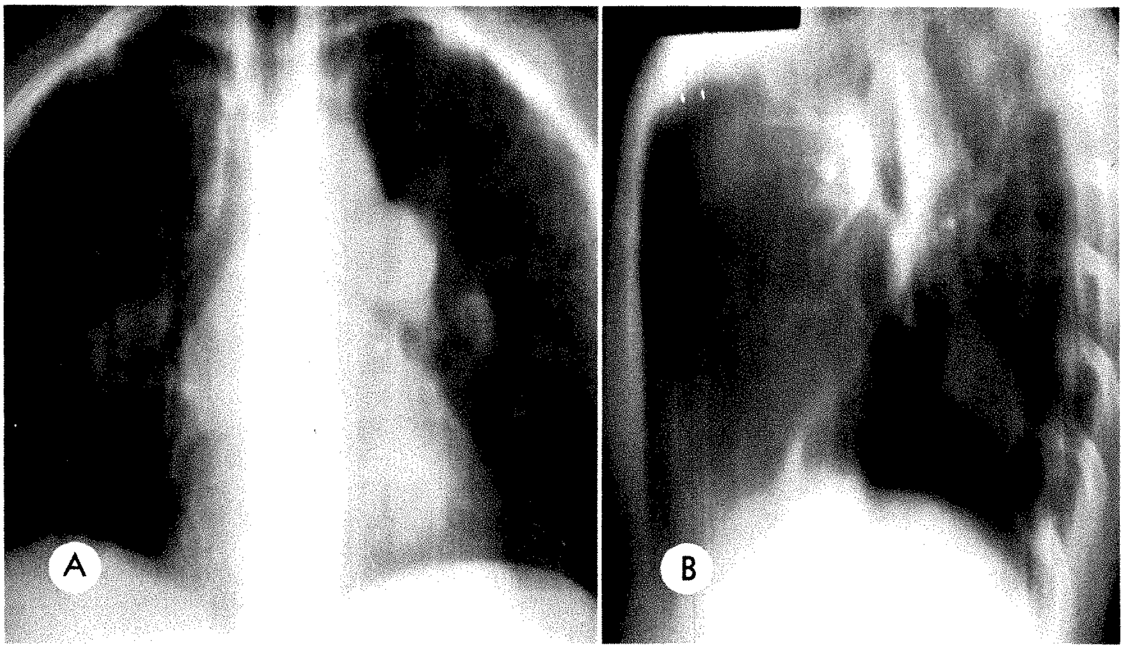

Fig. 2. Case 1. (*A*) Frontal and (*B*) lateral laminagrams showing the round and fusiform shaped masses to better advantage, but it is still impossible to differentiate between tumors and vascular lesions.

20. The lungs were clear on percussion and auscultation. There were no murmurs, no thrill and no clinical evidence of cardiomegaly. There was a slight clubbing of the fingers. Laboratory data were within normal limits. Blood cultures were sterile. Chest roentgenograms (Fig. 4, *A* and *B*) showed a normal heart and multiple round and fusiform masses along the mediastinum, the distal one in the right lower lobe. Laminagrams (Fig. 5) showed the masses in better detail. There was no evidence of a breakdown within the masses. While in the hospital the patient had intermittent low grade fever and grossly bloody sputum. Neoplasm, primary in the lung or metastatic, was strongly suspected. The search for a primary lesion was not rewarding. Bronchoscopy revealed the orifices of the right upper lobe, the left main bronchus, and segmental orifices to be displaced medially. A bronchial smear showed Class II cells. A scalene lymph node biopsy was reported as granuloma. Gastrointestinal and urinary tract examinations were normal. Blood cultures were negative. Alpha streptococci, Neisseria, coagulate positive staphylococci and hemophilus were isolated from the sputum.

During an exploratory thoracotomy, masses

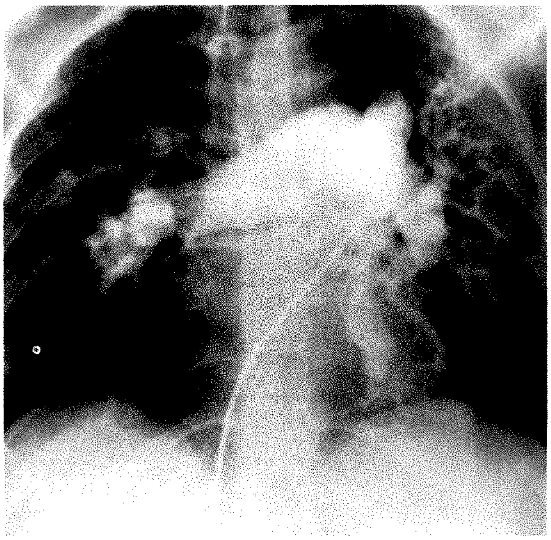

Fig. 3. Case I. Angiogram showing the catheter in the pulmonary artery. The selected early frame demonstrates simultaneous filling of the pulmonary artery and of the "masses" along the secondary and tertiary branches of the artery. Multiple mycotic aneurysms were palpated during thoracotomy for repair of the patent ductus arteriosus.

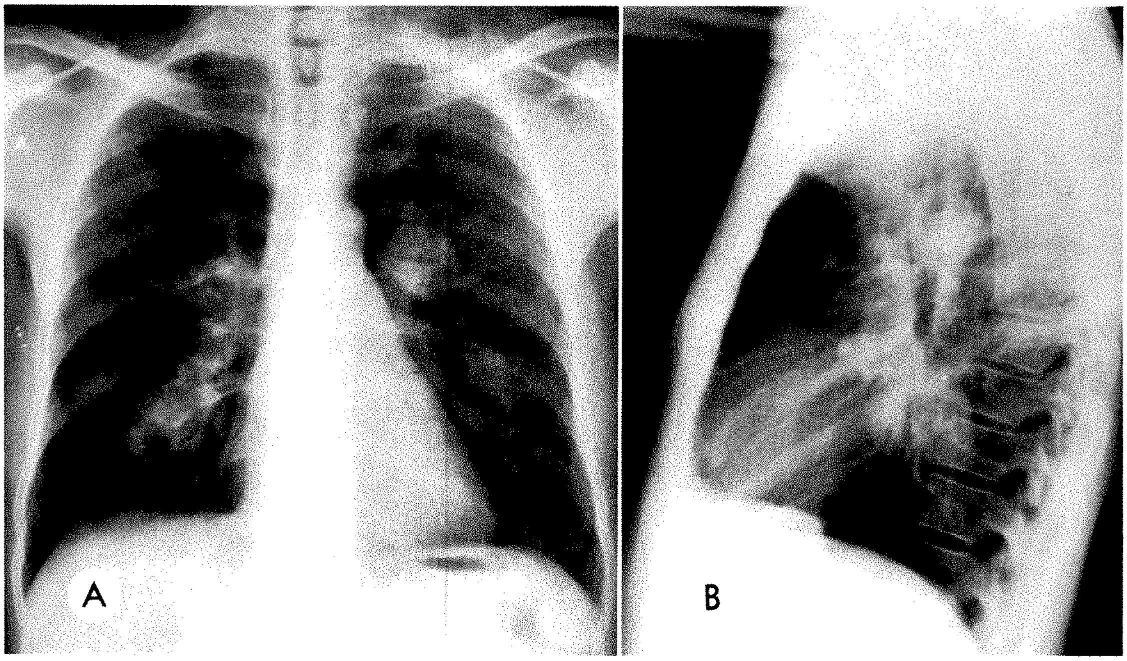

Fig. 4. Case II. (*A*) Posteroanterior and (*B*) lateral chest roentgenograms of a patient who developed masses in the lungs after a long standing and poorly treated purulent pulmonary infection. Note the normal heart size.

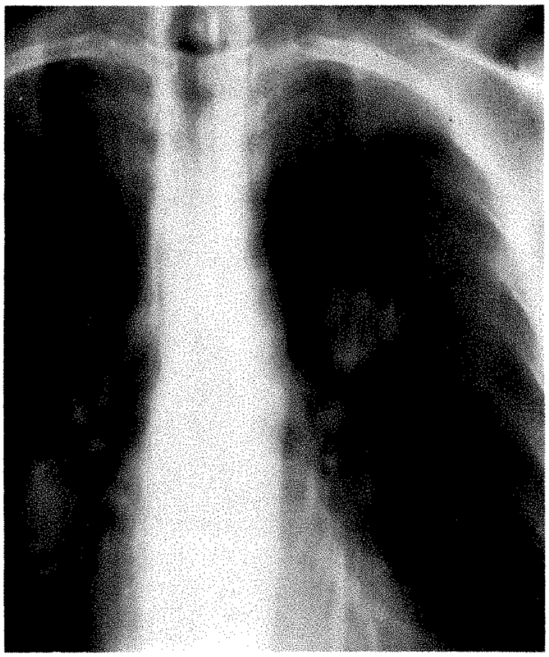

Fig. 5. Case II. Frontal laminagram showing the round and fusiform masses, arranged like fruit on a small tree, distributed around the hili.

in the right lower and right middle lobe were found and incised, resulting in massive bleeding. No biopsy could be obtained. After the patient recovered from the surgical procedure, a venous angiocardiogram was made (Fig. 6). As in Case I, the pulmonary artery and the masses filled with contrast material simultaneously. All masses seen on the plain roentgenograms and laminagrams filled and remained filled even during the late venous phase. No arteriovenous shunt was demonstrated. It was concluded that multiple mycotic aneurysms had developed along the branches of the pulmonary artery by direct propagation or lymphatic spread from a purulent focus or foci in the lungs.

Pulmonary function studies done 2 months after surgery showed a rise of pO_2 to about 93 per cent which was interpreted as evidence of a small arteriovenous shunt, probably resulting from the incision of one or the other of the aneurysms or as a result of the infection within or around an aneurysm.

Two months later the patient was rushed back to the hospital because of a massive hemoptysis, which occurred at home where he had been slowly improving with antibiotics and prednisone. He expired in the Emergency Room.

The autopsy disclosed multiple bilateral intrapulmonary mycotic aneurysms of the pulmonary arteries, with thrombosis and bacterial vegetations. One of the aneuryms of the lingula had eroded into a bronchus, thus causing a massive terminal hemoptysis and aspiration of blood. In addition, a massive subacute bacterial endocarditis involving the mural endocardium of the right ventricle and the septal leaflet of the tricuspid valve was found.

Comments. Case I was associated with subacute bacterial endocarditis superimposed on a patent ductus arteriosus. Alpha hemolytic streptococci were isolated in the blood cultures. Case II was associated with a massive subacute bacterial endcarditis involving the right heart. Both patients had exploratory thoracotomies and the aneurysms were seen and palpated, but could not be biopsied because of bleeding or fear of bleeding. Both cases are considered to represent mycotic type of multiple pulmonary artery aneurysms.

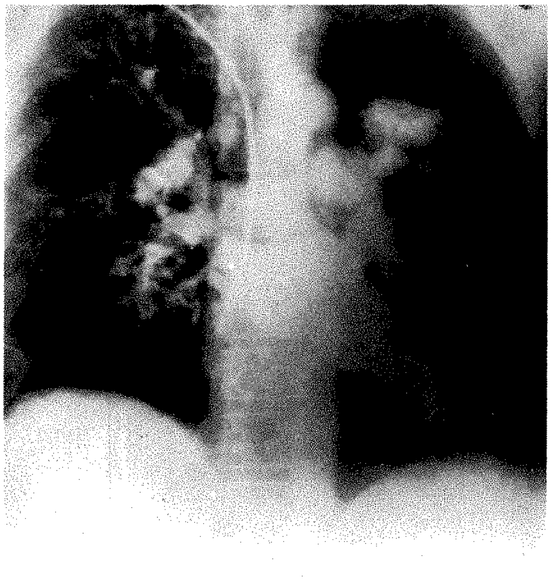

Fig. 6. Case II. Angiogram during the venous phase showing the retention of contrast material in the aneurysms. This is attributed to the lack of elasticity of the mycotic, degenerated segments of the artery. Note the origin and distribution of the branches of the pulmonary veins. They do not originate from the masses as they would in arteriovenous fistula.

DISCUSSION

Aneurysms of the pulmonary artery are well recognized as an entity by Good[4] in his discussion of the vascular abnormalities of the lung. They can occur in a major branch or in one or more branches of secondary or tertiary character.[3] By the end of 1962, 158 cases of major branch aneurysms had been reported in the medical literature according to Isemein *et al.*[5] Aneurysms of the small branches are rare. Reports of only 32 cases have been published thus far, 31 of which were reviewed by Charlton and du Plessis[3] and 1 was reported by Kopp and Green.[6] Of the published cases only a limited number had angiographic studies and only a few had bilateral or multiple involvement. Seventeen were positively mycotic, 4 were questionably mycotic, 8 were congenital, 1 was syphilitic, 1 traumatic and 1 was due to embolization of suture material from a repaired patent ductus arteriosus. Thus, 60 per cent of these aneurysms were due to mycotic degeneration of artery walls.

It is accepted that the most common cause of mycotic aneurysms in young individuals is subacute bacterial endocarditis, followed by old rheumatic valvulitis[7]. Subacute bacterial endocarditis usually accompanies a congenital defect such as patent ductus arteriosus, ventricular septal defect or atrial septal defect.[3,8,9,12]

In elderly people there is usually a direct extension from a neighboring suppurative focus, commonly due to *Staphylococcus, Streptococcus* or *Salmonella.*[2]

The pulmonary artery can be invaded by emboli via the vasa vasorum branches of the bronchial artery which are part of the systemic circulation.[3] A second possibility is lodgement of the septic emboli in the lumen of the arteries and direct invasion of the intima. The third manner of invasion is erosion by an adjacent suppurative process directly or through the perivascular lymph channels.[9] As a result of the bacterial invasion there is destruction of the intima and the elastic and muscle fibers, and their replacement by fibrous connective tissue.[6,7]

The weakened arterial wall yields and becomes dilated.[9] Rupture can take place, and a hematoma may organize into a false aneurysm. Rupture in a vein can occur and create a shunt. The end result is fibrosis of the arterial wall with, at times, active endarteritis.[11]

Clinically, mycotic pulmonary artery aneurysms follow a febrile course. The most frequent manifestations are cough, hemoptysis, chest pain and dyspnea. There is no cyanosis; occasionally there is clubbing of the fingers. Associated peripheral embolic manifestations and thrombosis have been reported as a source or consequence of infection.[6,7]

ROENTGEN MANIFESTATIONS

Usually multiple aneurysms of the pulmonary artery are indistinguishable from inflammatory or neoplastic lesions on plain roentgenograms (Fig. 1, *A* and *B;* and 4, *A* and *B*). If the distribution of the "masses" is close to the mediastinum, mediastinal lymphadenopathy due to tuberculosis, sarcoidosis or lymphoma may be suspected. If the "masses" are more peripheral, metastatic disease may be considered. Multiple abscesses are often diagnosed, particularly if the patient's course is febrile.[8] In the case that vascular lesions are suspected, aneurysms, arteriovenous fistulae, the so-called varix and intralobular bronchopulmonary sequestration should be considered. Fluoroscopically, all vascular lesions pulsate, in contrast to inflammatory and neoplastic masses, although the latter could possibly transmit pulsations. On laminagrams multiple oval or fusiform masses are usually demonstrated, arranged like fruit on a small, short tree (Fig. 2, *A* and *B;* and 5). The bronchi are generally normal[6] but can be displaced. Calcium is seldom seen in multiple mycotic aneurysms. No areas of breakdown or fluid level are seen in the individual "masses."

To differentiate, however, between tumors and vascular lesions angiography is necessary and ordinarily a venous angiogram should be made. The catheter can be left in the right atrium (Case II) or advanced to the pulmonary artery (Case 1). The contrast material opacifies the "masses" simultaneously with the opacification of the pulmonary artery (Fig. 3 and 6). The aneurysms usually opacify at the same time and stay filled even through the venous phase. This is attributed to a slow emptying due to lack of elastic tissue in the vessels at the point of the aneurysmal dilatation. No veins associated with the "masses" are demonstrated.

The interpretation of such an angiogram requires a systematic elimination of all possible vascular abnormalities. Aneurysms of the pulmonary vein or the so-called varix would opacify only during the venous phase of angiography.[4] In arteriovenous fistulae[10] the contrast material opacifies an enlarged vessel leading to the sac, followed by opacification of an enlarged vein leading back to the hilus. The sacs filled with contrast material empty quickly by shunting. The left atrium is visualized early in the procedure.[4] The rare systemic-to-pulmonary fistulae and also intralobular bronchopulmonary sequestration are opacified only by thoracic aortography via the bronchial arteries. The same opacification would be expected for highly vascular metastatic tumors.

The real difficulty lies in distinguishing acquired from congenital aneurysms. Barnes and Stedem[1] have suggested that pre-existing congenital aneurysms of the pulmonary artery can enlarge considerably by a superimposed infectious process. The patient's background and course can be of help.

CONCLUSION

Two cases of multiple pulmonary artery aneurysms involving small branches are presented. They are presumably mycotic: one related to subacute bacterial endocarditis with patent ductus arteriosus, the other to massive subacute bacterial endocarditis involving the right ventricle and the tricuspid valve. Thirty-two similar cases, more than half of them mycotic, have been reported thus far. In only a few isolated cases were laminagraphy and angiography performed and only a few were diagnosed before surgery or death. The etiopathology, roentgen manifestations and differential angiographic diagnosis of multiple pulmonary artery aneurysms are briefly discussed.

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PERCUTANEOUS TRANSCAROTID THORACIC AORTOGRAPHY*

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THE value of thoracic aortography in the diagnosis of certain cardiovascular and noncardiovascular lesions has been well established.[1] Congenital lesions of the heart and great vessels,[3,4] thoracic aortic aneurysms,[19,20] acquired lesions of the aortic valve,[13,14] the coronary arteries,[12,18] mediastinal tumors,[5] and most recently occlusive disease of the aorta and its branches[9] have been studied by this method.

The very fact that a number of techniques exist for performing thoracic aortography is an indication that no single method has enjoyed uniform success. High quality aortograms have been obtained by retrograde catheterization using either the brachial or the femoral arterial route. However, the use of these vessels is not always feasible when dealing with patients having extensive arteriosclerosis or when complete or incomplete occlusions are present (Fig. 1, *A* and *B*). Cronqvist,[6] for example, was successful in passing a catheter in a retrograde fashion from the femoral artery in 92 per cent of the patients under 40 years of age, but in only 50 per cent of patients over 50 years of age.

Our occasional inability to successfully introduce a catheter into the thoracic aorta, either because of the presence of obstruction or tortuosity in the aorto-iliac or subclavian areas, prompted us to turn our attention to the common carotid artery. Jönsson *et al.*[10,11] have expressed concern for the use of this latter artery for aortography. However, their conclusions were based upon experiences with a metal cannula rather than the flexible catheters now in use.

The technique to be described is safe and easily performed. The transcarotid technique was initially used only in those patients in whom proximal thoracic aortography had been unsuccessful when using the brachial and femoral arteries for catheter insertion. As further experience revealed certain distinct advantages of this approach, it has replaced other approaches for the study of the proximal aorta and its major branches in this institution.

TECHNIQUE

The technique employed for performing this examination is carried out as follows:

1. The appropriate area of the neck is shaved if necessary, scrubbed with an aqueous ceepryn 1–100 solution for 10 minutes, painted with two coats of tincture of ceepryn, and draped with sterile towels.

2. The skin and subcutaneous tissue at the proposed site of needle insertion, slightly below the carotid bifurcation, are infiltrated with a local anesthetic (Fig. 2*A*). General anesthesia has usually not been necessary but may be indicated in the apprehensive or uncooperative patient.

3. A thin-walled short-beveled No. 18 gauge needle is inserted into the common carotid artery a short distance below the bifurcation and directed inferiorly (Fig. 2*B*). This needle has been found to be less cumbersome than the Seldinger needle. Following this, an 80 cm. guide wire* with a flexible tip is passed proximally for a distance of at least 3 inches beyond the needle tip to prevent its removal with the needle (Fig. 3*A*). The needle is then removed leaving the guide wire in place.

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* Schick X-ray Company, Chicago, Illinois.

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The guide wire must pass easily into the vessel, and only very gentle manipulation should be used. If resistance is encountered it should be pulled back slightly and further gentle manipulations used to properly position it in the lumen of the artery. The introduction of a guide wire in the face of resistance may lead to perforation of the posterior wall of the artery or breaking of the guide wire at the point of attachment of the flexible tip.

4. A catheter of teflon tubing* is then placed over the guide wire and advanced into the arterial lumen (Fig. 3*B*). When blood flows freely from the catheter, the guide wire is removed and the catheter advanced to the desired position (Fig. 3*C*).

The tubing used in the preparation of this catheter has an inner diameter of .059 and outer diameter of .083 inch. This rather large ratio of lumen to over-all diameter permits rapid delivery of contrast medium with a relatively small catheter. The catheter, pre-cut to measure 20 inches, is tapered at one end by slight heating, flanged at the other end with a pre-heated Kifa flanging tool† and attached to an adapter. Generally, several side holes are placed in the distal 3 inches of the catheter to ensure rapid delivery of the contrast medium and to avoid backlash. Chemical, gas, or heat sterilization techniques may be used in the preparation of the catheters. In most instances it is possible to connect the adapter directly to the mechanical injector, thus eliminating the need for a connecting tube.

By filling the catheter with contrast medium and using fluoroscopic control, the tip can be positioned very precisely in the root of the aorta. More often, however, we have relied on catheter measurements based on values obtained from a study of cadavers. The average distance from the com-

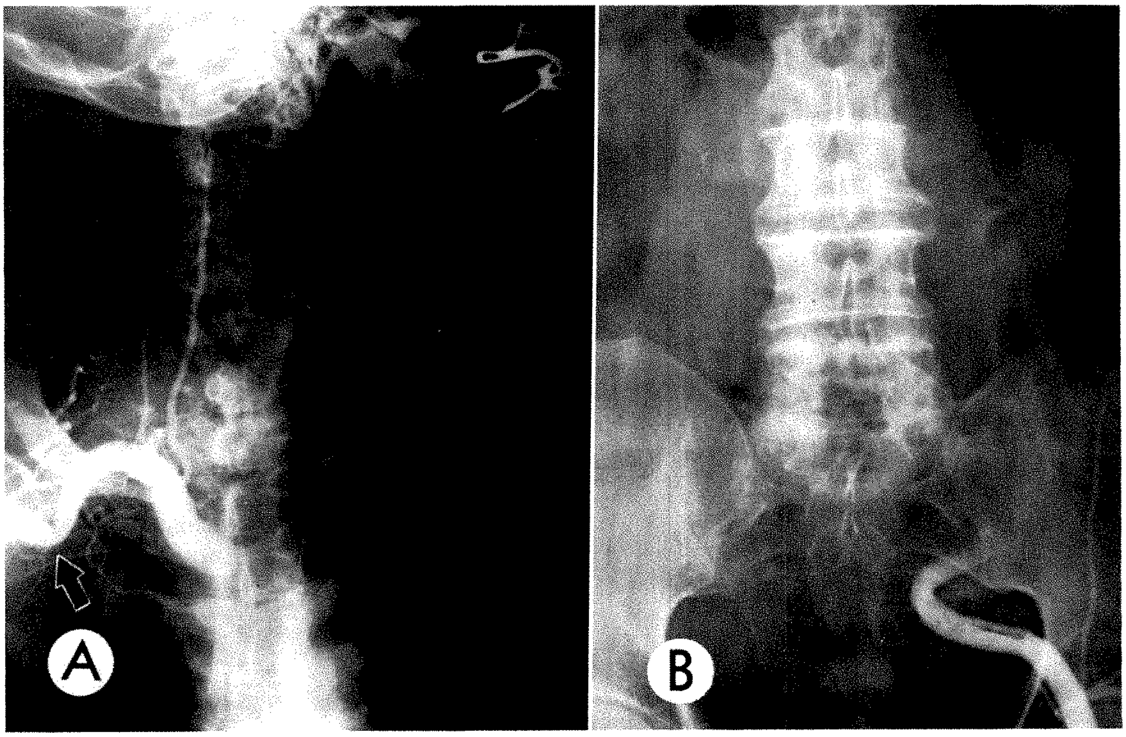

Fig. 1. (*A*) A marked kink of the subclavian artery (arrow) prevents passage of the catheter. Injection of contrast medium was made distal to the kink. (*B*) Marked tortuosity and atherosclerosis of external iliac artery prevents catheter passage into the aorta.

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* Teflon tubing available in various diameters from Sparta Manufacturing Company, Dover, Ohio.

† Schick X-ray Company, Chicago, Illinois.

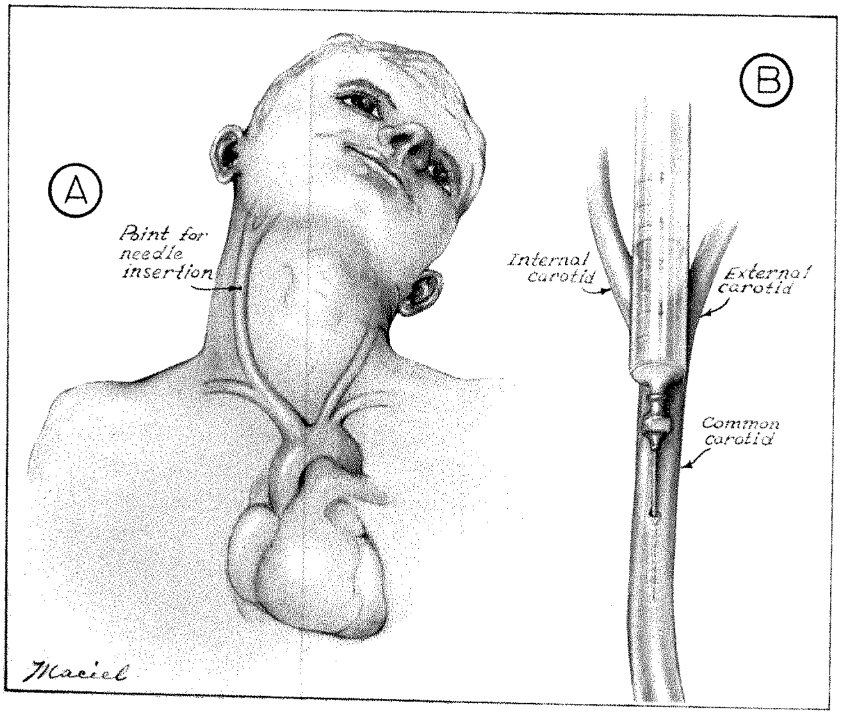

Fig. 2. (*A*) Site of needle insertion slightly below carotid bifurcation. (*B*) A thin-walled, short-beveled No. 18 gauge needle is inserted into the common carotid artery a short distance below the bifurcation and directed inferiorly.

mon carotid bifurcation to the aortic valve is approximately 10 inches. After positioning the catheter, a scout roentgenogram should be obtained at the time of injection of a small dose of contrast medium. This has the combined advantage of a test for sensitivity to the medium and assurance of accurate positioning of the patient and catheter. Generally, a 15–20 degree right posterior oblique projection is utilized. Occasionally, a left posterior oblique view is necessary to adequately visualize the bifurcation of the innominate artery.

The contrast medium is delivered by a mechanical pressure injector.* The pressure used with the Taveras injector is usually 875 pounds per square inch, and with the Gidlund injector, 8 kilograms per square centimeter. We have used 50–60 cc. of ditriokon† for most of the studies; however, other media having similar characteristics may also be used. The innominate, right carotid, and right subclavian arteries can be better evaluated by withdrawing the catheter into the proximal common carotid artery and performing a second injection manually (Fig. 4). For this second phase of the study, 10–12 cc. of hypaque** 50 per cent has been used. A pressure injector for this latter study results in the loss of significant amounts of contrast medium into the aortic arch and is therefore not used.

A Schönander film changer is used for obtaining serial roentgenograms. Single film technique, however, has been adequate when the injection is made in branch vessels rather than in the aorta.

Following completion of the study and removal of the catheter, moderate pressure is applied to the area for approximately 10 minutes to obtain hemostasis.

RESULTS

During the past year we have obtained thoracic aortograms using this method in 52 patients without technical failure. Diagnostic roentgenograms have been obtained in each instance (Fig. 5 through Fig. 9). We are entirely satisfied that it is a safe and useful procedure, not only for patients in whom retrograde catheter passage by other routes is not possible, but also for more widespread use as the preferred route for catheter insertion.

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* Taveras Model, Picker X-ray Corporation, White Plains, New York *or* Gidlund Model, Elema-Gidlund Company, Stockholm, Sweden.

† Sodium diprotrizoate, sodium diatrizoate.

** Sodium diatrizoate.

There have been no cerebral complications following these studies and thrombosis of the common carotid arteries at the point of catheter insertion has not occurred. Approximately one-half of these patients have had significant hypertensive cardiovascular disease in addition to peripheral arteriosclerosis. In view of this high incidence of hypertension, there was initial concern that this technique might result in the accumulation of large hematomas following removal of the catheter. In this study only 2 patients developed small hematomas at the site of catheter insertion which required no further treatment. As a rule, edema of the neck following these studies has been less than that noted with the use of percutaneous needle techniques.

In most of the studies to date the right common carotid artery has been used for catheter insertion. The majority of these patients have had clinical findings suggestive of aortic arch occlusive lesions, and the use of this artery rather than the left common carotid has given additional information concerning the patency of the innominate, carotid, subclavian and vertebral arteries on the right side. The left common carotid artery has been used in a few patients when a partial or complete occlusion of the innominate or of the right common carotid artery itself was suspected. A significant diminution of pulsation in the right common carotid artery or right brachial artery, especially when associated with a diminished blood pressure in the right arm, suggests a proximal occlusive lesion such as in the innominate artery. The presence of

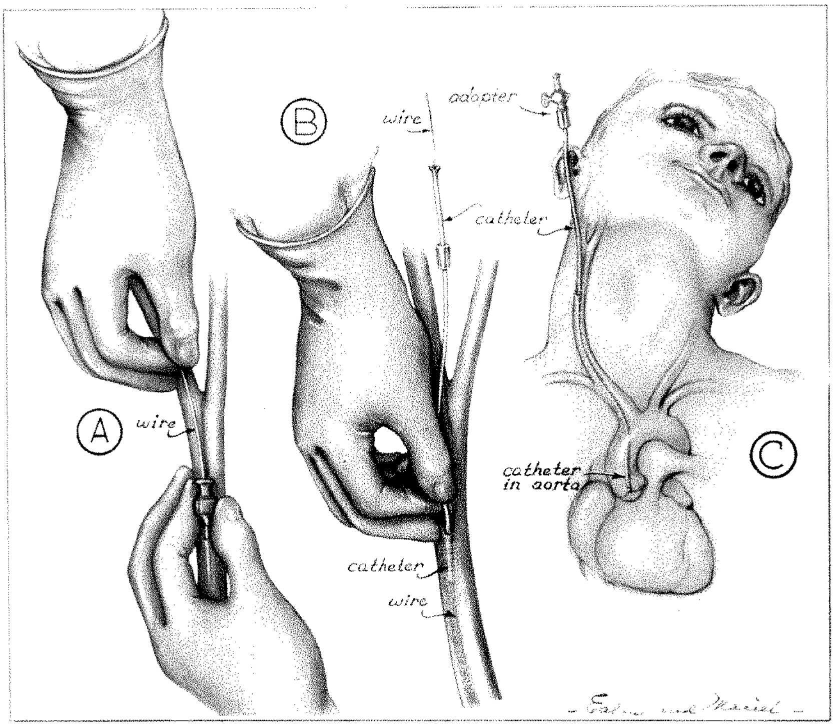

Fig. 3. (*A*) An 80 cm. thin guide wire with a flexible tip is passed proximally for a distance of at least 3 inches beyond the needle tip to prevent its removal with the needle. (*B*) A catheter of teflon tubing is then placed over the guide wire and advanced into the arterial lumen. (*C*) When blood flows freely from the catheter, the guide wire is removed and the catheter advanced to the desired position.

these signs would weigh in favor of using the left common carotid artery for catheter insertion.

Since the adoption of the teflon catheter, more than 400 examinations using the carotid or femoral arteries have been performed without thrombosis. Only 3 occlusions have occurred during the performance of more than 250 brachial artery catheterizations. Further treatment was not required in these 3 instances, since neither subjective nor objective evidence of circulatory embarrassment resulted. The use of the brachial artery with its smaller diameter was probably a contributing factor in the development of this complication. This rather low incidence of complication has strengthened our confidence in the safety of the use of the common carotid artery for catheter insertion. The technique has been used safely in patients with known complete contralateral common carotid artery occlusion.

ADVANTAGES OF TRANSCAROTID AORTOGRAPHY

The principal advantages of the transcarotid technique described in this report are as follows:

1. The technique is easly performed. It is possible to complete a study in approximately 30 minutes.

2. By withdrawing the catheter from the proximal aorta and placing it in the proximal common carotid artery, it is possible to obtain simultaneous visualization of the innominate, right subclavian, right carotid, and right vertebral arteries. Visualization of the intracerebral distribution of the latter two generally requires a second injection of contrast medium.

3. The positioned catheter does not limit movement of the patient for obtaining rotational views.

4. The use of the carotid artery for thoracic aortography permits the use of a significantly shorter catheter than when using the femoral or brachial arteries. Distances from the brachial artery at the antecubital crease, femoral artery at the inguinal ligament, and common carotid artery bifurcation to the aortic valve were measured in 15 cadavers by actual catheter insertion under direct vision during routine postmortem examination. The average distances noted were 23, 25, and 10 inches respectively. Poiseuille's law states in part that velocity of flow of fluid through a rigid tube is inversely proportional to its length. Thus, it is evident that more rapid delivery of contrast medium is possible by using the transcarotid technique. Studies in this institution[8] have shown that by simply shortening catheter length from 30 to 10 inches, all other factors being equal, a 25 per cent increase in delivered bound iodine in milligrams per second of contrast medium occurs.

5. This technique adds safety factors over cutdown methods in that there is less arterial intimal damage. Perhaps of equal importance is the fact that blood flow con-

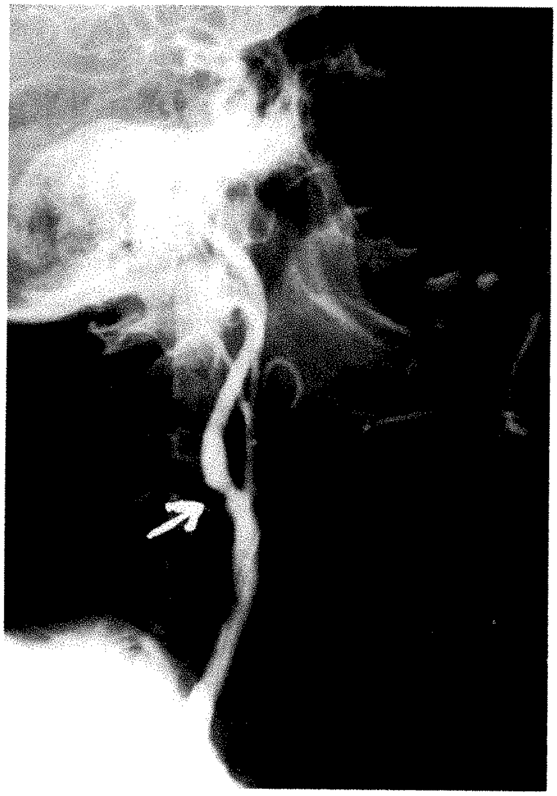

Fig. 4. The catheter has been withdrawn into the proximal common carotid artery. A manual injection of 12 cc. of contrast medium demonstrates a plaque of the internal carotid artery (arrow) and good filling of cerebral vessels.

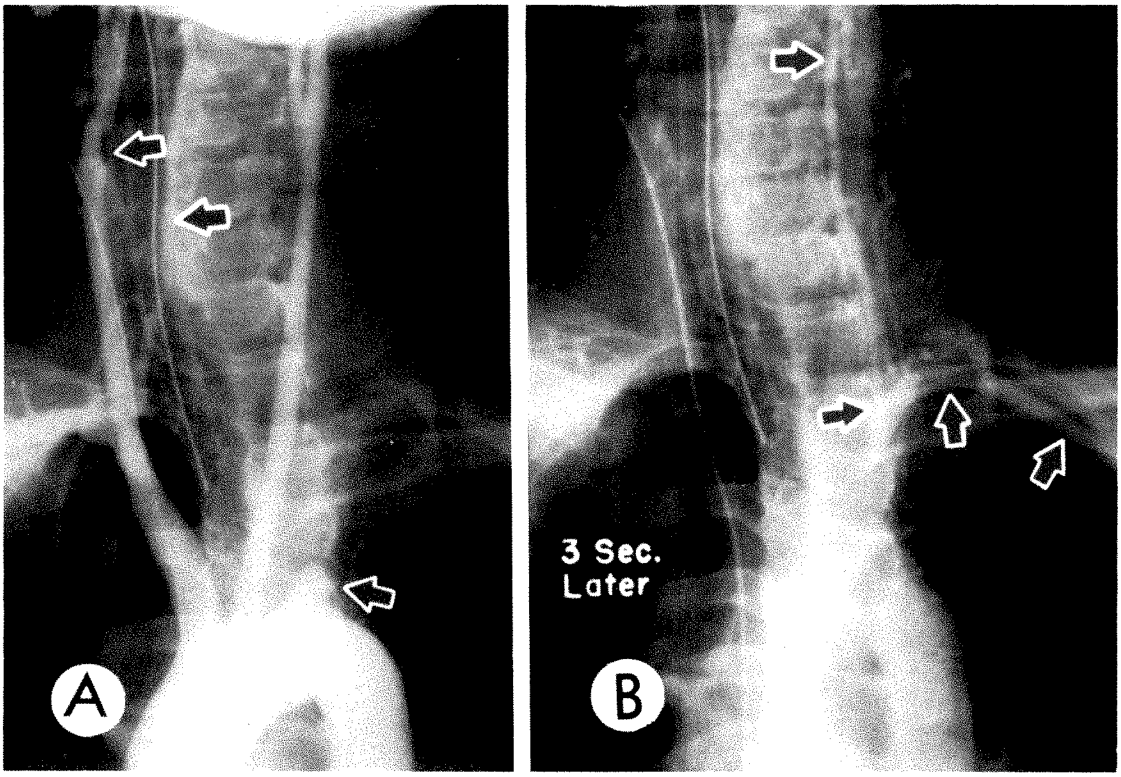

FIG. 5. (*A*) Complete occlusion of the left subclavian artery. Both the right and left common carotid arteries as well as the right vertebral artery are well demonstrated. (*B*) The left subclavian artery is filled by retrograde flow down the left vertebral artery—subclavian steal syndrome.

tinues through the artery when the catheter is in position. This latter factor has obvious advantages.

6. A high rate of successful studies is possible due to the fact that the arteriosclerotic involvement of the common carotid artery proximal to its bifurcation is generally less than other arteries that have been used for catheter insertion.[7]

DISCUSSION

The technique of retrograde catheter aortography was introduced by Radner[15] in 1948. His method required surgical dissection of the artery to be used and was therefore time-consuming and potentially hazardous. The introduction of a percutaneous method of passing a catheter over a steel spring wire by Seldinger[16] in 1953 immediately expanded the usefulness of the technique. This latter modification was quickly accepted and adapted to the particular vessel in which the clinician was interested.

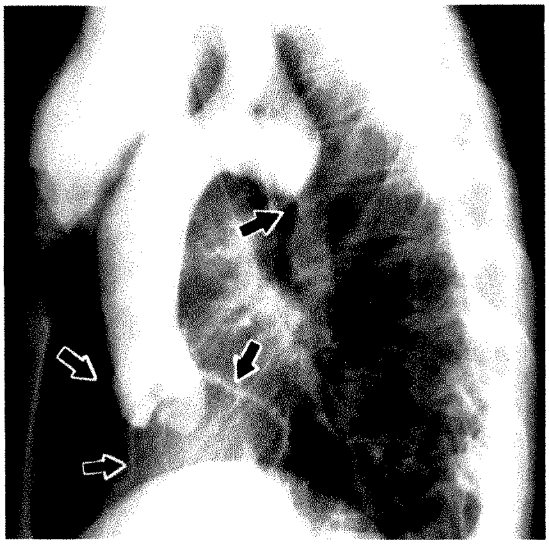

FIG. 6. Complete occlusion of the aorta secondary to coarctation just distal to anomalous right subclavian artery.

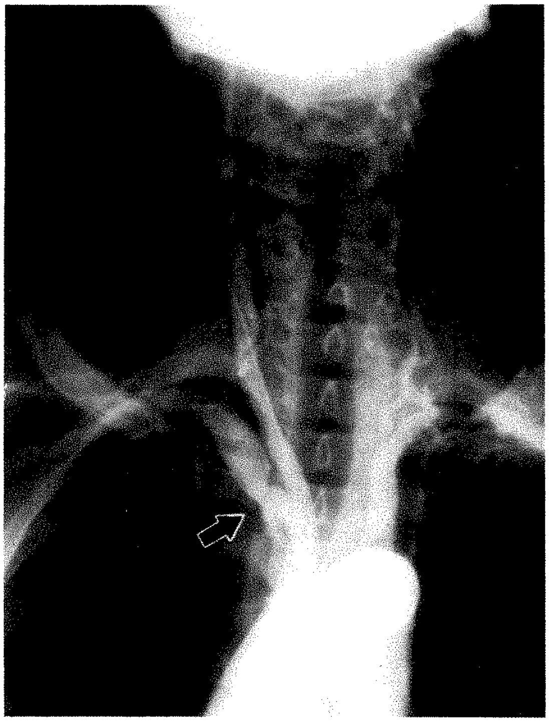

Fig. 7. Arch study in a 32 year old man following a right hemiplegia demonstrating extensive vascular disease. There is marked narrowing of the right subclavian artery. The left common carotid artery is occluded at its take-off from the aorta. The left vertebral artery is markedly narrowed at its origin and shows poststenotic dilatation. The left subclavian artery has a large plaque just distal to the thyrocervical trunk.

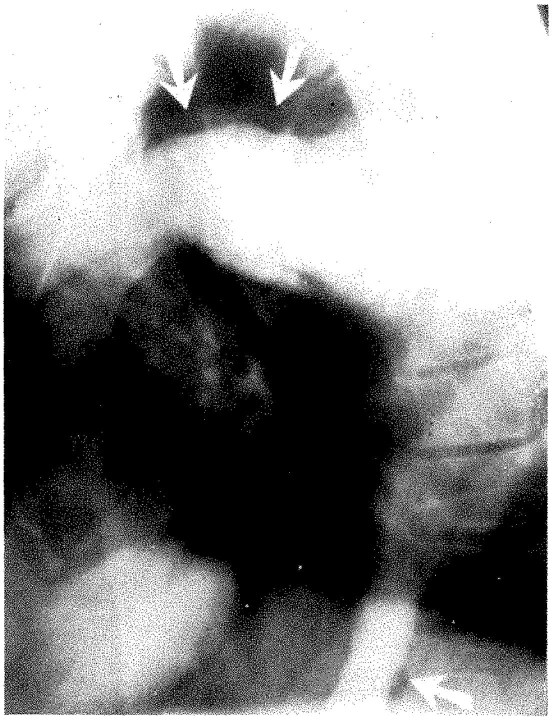

Fig. 8. Dissecting aneurysm of the aorta extending to the origin of the left subclavian artery. Note the double density (upper arrows) and the irregularity of the distal thoracic aorta (lower arrow).

The ease of performance and safety associated with this technique have now been well established.

The possibility of using the common carotid artery for percutaneous catheter insertion in arteriography has been previously explored by other investigators. However, certain differences exist between their techniques and the one described in this report, both in the method itself and in its application. In 1960 Berk[2] described a transcarotid technique for combined carotid-vertebral arteriography which he had used in 10 patients. The present technique differs from his in several important details. First, while we have retained the Seldinger principle for catheter insertion, we have discarded the equipment originally described in favor of that which is less cum-

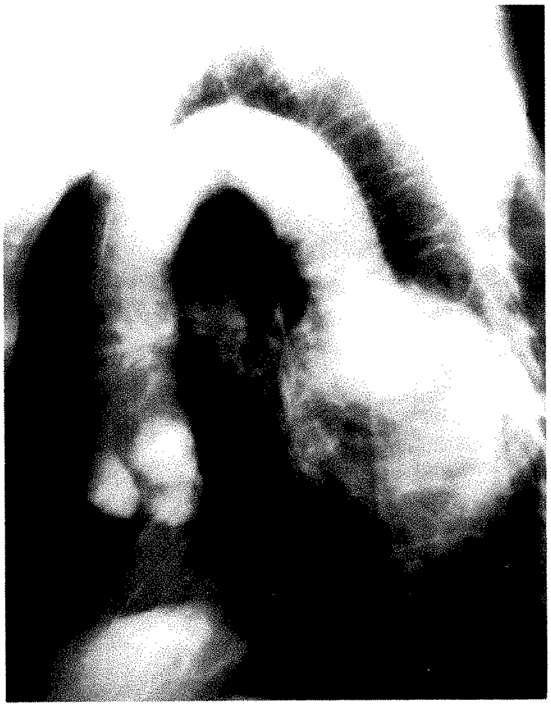

Fig. 9. Large saccular aneurysm of the descending thoracic aorta.

bersome and more efficient. Secondly, the application of the technique suggested by Berk, is, in our opinion, too limited since it applied only to the study of the cerebral circulation.

DeSaussure and Keirns[7] more recently have reported results in 103 arteriographic examinations of the cerebral circulation using the common carotid artery for catheter insertion. Failure to achieve proper catheter positioning and successful arteriography occurred in only 5 cases. The present technique described differs mainly in that its use is extended to visualize the proximal aorta and its branches, thus making the procedure applicable to a wider variety of lesions and areas.

Other investigators have used the transcarotid approach for proximal thoracic aortography following surgical dissection of the common carotid artery.[3,4,14] This technique has the obvious disadvantages inherent in any method requiring arterial dissection as already noted.

While the role of thoracic aortography in many vascular problems involving the proximal aorta has been well established, the importance of this diagnostic procedure in the study of cerebrovascular insufficiency has not been emphasized. As more information from the arteriographic study of patients having cerebrovascular insufficiency accumulates, it is apparent that the differentiation between basilar artery and carotid artery insufficiency is not always possible on clinical grounds alone.[17] Furthermore, the symptoms of patients having occlusive disease involving the brachiocephalic branches of the aorta may closely mimic those of patients having either basilar or carotid artery insufficiency. Thoracic aortography may be helpful in localizing these more proximal areas of occlusive involvement in patients having symptoms suggestive of cerebrovascular ischemia.

Haller and Turrell[9] have indicated that satisfactory visualization of the total cerebral circulation is possible by using the percutaneous retrograde femoral technique for proximal thoracic aortography. In our experience, satisfactory delineation of the distal extent and in particular the cerebral distribution of the carotid and vertebral arteries has not been possible with an arch study alone. Furthermore, evaluation of collateral circulation, an important factor when considering cerebrovascular ischemia, cannot be made accurately when all vessels are simultaneously filled.

In cases where it is desirable to evaluate the total cerebral circulation by the use of the technique described, the only arteries which require additional study are the intracerebral distributions of the left common carotid and the left vertebral arteries. The thoracic aortogram obtained by the technique described has been adequate to visualize the origin and the cervical portions of the left carotid and left vertebral arteries. For intracerebral visualization of these two arteries, a percutaneous needle technique is used for the former and a retrograde catheter technique for the latter.

When consideration is given to a specific artery for percutaneous catheter insertion, the effects of a possible complicating thrombosis must be taken into account. In the case of the carotid artery, the occurrence of a thrombosis may lead to serious neurologic damage. We are convinced, however, that by using a teflon catheter of the size mentioned in this report the procedure can be safely performed. Studies here[8] with the usual injection technique have shown that increasing the internal diameter of a catheter beyond .059 inches results in only minor increases in delivery rate of the contrast medium. Moreover, the use of a catheter with an over-all diameter greater than .083 inch results in greater damage to the arterial wall and a higher incidence of hematoma formation in the neck.

Although we have not used the transcarotid technique for coronary arteriography, the opacification of these vessels in many of the cases suggests that the method could be adapted for these studies. The use of this technique for abdominal aortography, where femoral artery catheter insertion is not feasible, has been successful. For abdominal aortography the catheter can easily be directed, by the guidance of fluoroscopy, into the descending thoracic aorta.

SUMMARY

The technique of percutaneous transcarotid thoracic aortography is safe and easily performed. Its use is particularly applicable to those patients where the transfemoral or transbrachial approaches are not possible, but may be employed in other patients as the preferred initial route. Diagnostic roentgenograms have been obtained in all patients studied and no serious complications using this technique have occurred.

ADDENDUM

Since the preparation of this manuscript, thoracic aortography has been performed using the described technique in an additional 25 patients without complications.

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We are grateful to Dr. Ronald Fegelman, senior resident in surgery, for performing retrograde arterial catheterizations in cadavers during postmortem examinations. The measurements obtained were of great value to this study. We are also deeply indebted to Dr. Benjamin Felson, Professor and Chairman of the Department of Radiology, for his encouragement and many helpful suggestions in the preparation of this paper.

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COLLATERAL CIRCULATION ASSOCIATED WITH OCCLUSION OF THE PROXIMAL SUBCLAVIAN AND INNOMINATE ARTERIES*

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AS THE aging population increases, cerebrovascular occlusive disease becomes a greater medical and surgical problem. Recent advances in reconstructive vascular surgical techniques made the need for angiographic demonstration of these lesions indispensable.

Systematic angiography of the aortic arch and brachiocephalic vessels in patients with suspected cerebrovascular disease has shown that marked stenosis or occlusion of the proximal subclavian artery is relatively common.

METHOD

Recently, at the University of California (San Francisco) the aortic arch and its branches have been examined angiographically in all patients with suspected cerebrovascular insufficiency. The vessels were visualized via the percutaneous transaxillary route as described previously.[4] Usually, contrast medium is first injected through a catheter inserted into the ascending arch of the aorta, using the right transaxillary approach. Serial roentgenograms are obtained with the patient in the anteroposterior and right posterior oblique positions. The catheter is then withdrawn into the right subclavian artery to visualize the right carotid and vertebral basilar intracranial circulation. Left carotid arteriography is performed as a separate study.

MATERIAL

In the past 8 months, 115 patients with symptoms of cerebrovascular insufficiency underwent complete angiographic study of the aortic arch and its branches. Of these, 15 (6 women and 9 men) were found to have marked stenosis or occlusion of the proximal portion of one of the subclavian arteries. In 1 of the men, in addition, the innominate artery was occluded. The ages of these 15 patients ranged from 44 to 70 years. Their symptoms included confusion, dizzy spells, dysarthria, vertigo, headaches, hemiparesis, visual disturbances, and syncopal attacks. Four patients complained of easy fatigue of the affected arm.

A significant difference in blood pressure in the two arms was observed in all patients. Ischemic symptoms in the involved hand were noted only in the patient with innominate artery occlusion. In all patients, however, the pulse in the affected arm was weak or absent. The occlusion was segmental in all instances and the distal subclavian artery was filled via collateral channels. At operation all the occlusive lesions were found to have resulted from local atherosclerotic disease. Associated arteriosclerotic narrowing or occlusion of the extracranial carotid or vertebral arteries was noted in most patients (Fig. 1 and 2*A*; Table 1). In only 2 patients was the occlusion of the subclavian artery the only evidence of significant atherosclerotic disease (Case 11 and 12). The proximal subclavian artery was completely occluded in 12 patients. Marked stenosis of the left subclavian artery was observed in 4 patients. One patient had both an occlusion of the right subclavian and a marked stenosis of the left subclavian arteries. Another patient (Case 15) had innominate artery occlusion and marked stenosis of the left subclavian artery. The left subclavian artery was involved in 12, and the right in 4. These observations confirm the previ-

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ously reported higher incidence of left-sided subclavian occlusion.[7]

COLLATERAL CIRCULATION

With occlusion of the proximal subclavian artery, blood may reach the arm by one of several pathways.[5]

I. REVERSAL OF VERTEBRAL ARTERY BLOOD FLOW TO SUPPLY THE DISTAL SUBCLAVIAN ARTERY[1,2,3,6]

a. Vertebro-vertebral pathway (Fig. 2 through 4, inclusive). With well developed vertebral arteries, a preformed collateral channel allows the blood to reach the distal subclavian artery by reversed flow down the ipsilateral vertebral artery. This route of collateral flow was observed in 12 of our patients and represents the most frequent, and also, potentially the most dangerous pathway. In 1 patient with occlusion of the left subclavian artery, this collateral pathway was observed even though the proximal 4 cm. of the right vertebral artery was occluded. The distal right vertebral artery was filled by collateral arteries from the thyrocervical trunk. Serial roentgenograms showed a reversal of flow in the left vertebral artery to supply the left subclavian artery beyond a proximal occlusion (Fig. 5, *A*, *B* and *C*).

Normally, the blood pressure is greater at the origin of the vertebral artery than at the origin of the basilar artery, and the blood flows in a cephalad direction. Reivich and co-workers[6] stated that when the mean pressure at the origin of the vertebral artery equals that of the basilar artery, no blood flows through the vertebral artery. The flow in the ipsilateral vertebral artery ceases when the mean pressure in the distal subclavian artery is reduced by only 10 per cent. When obstruction is more severe and further reduces pressure of the distal subclavian artery, flow in the vertebral artery will reverse. Blood then flows from one vertebral artery down the other vertebral artery into the subclavian artery (Fig. 6). By diverting blood from the vertebrobasilar circulation, the reversal of vertebral arterial flow may cause symptoms of cerebrovascular insufficiency. With associated arteriosclerotic involvement of the carotid arteries which prevents adequate additional blood flow to the posterior circulation, the possibility of cerebral ischemia becomes greater. One patient could produce cerebral symptoms by prolonged exercise of the involved arm. In this case, the exercise probably increased the flow of blood to the arm, shunting it away from the brain.

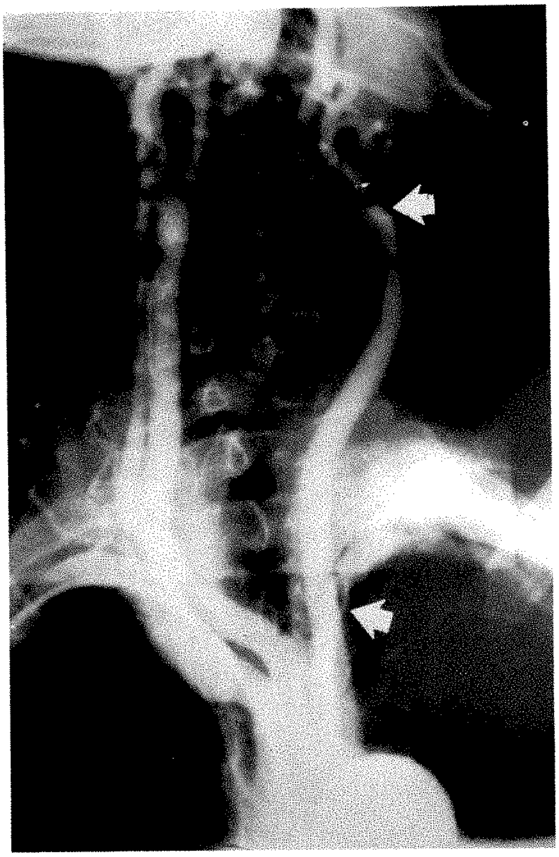

Fig. 1. Marked stenosis of left subclavian and left internal carotid arteries.

b. External carotid-vertebral anastomosis (Fig. 7, *A*, *B* and *C*). In this route, blood may reach the distal subclavian artery via anastomoses between occipital branches of the external carotid artery and muscular branches of the vertebral artery. The flow in the vertebral artery is then reversed. This pathway was observed in 2 patients (Case 4 and 8). It is important to recognize this collateral pathway since it may give the first clue at carotid arteriography

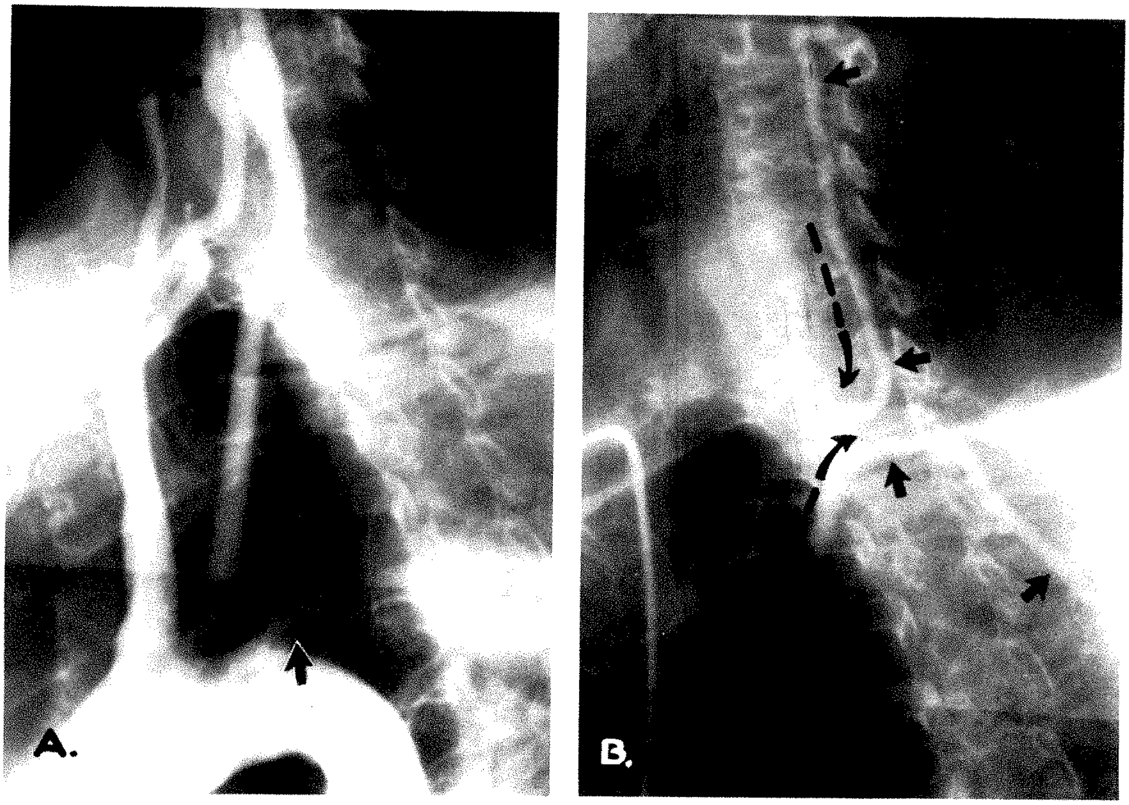

Fig. 2. (*A*) Complete occlusion of left subclavian and right internal carotid arteries. (*B*) Reversal of flow in left vertebral artery supplying distal left subclavian artery.

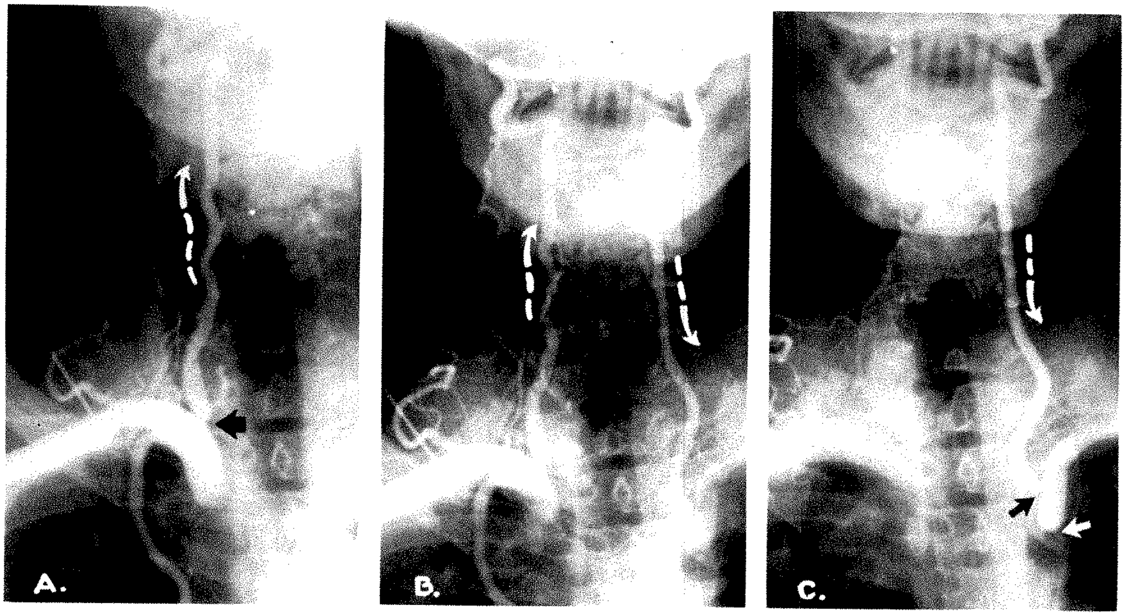

Fig. 3. (*A*, *B* and *C*) Occlusion of proximal left subclavian artery with vertebro-vertebral collateral channel. Stenosis at origin of both vertebral arteries.

Table I

ASSOCIATED EXTRACEREBRAL DISEASE IN PATIENTS WITH SUBCLAVIAN ARTERY OCCLUSION

Case No.	Age and Sex	Innominate Artery	Subclavian Artery		Common carotid Artery		Internal Carotid Artery		Vertebral Artery	
			Right	Left	Right	Left	Right	Left	Right	Left
1	63 M	0	0	occulsion	2+	2+	1+	2+	occlusion of proximal artery	0
2	70 F	0	0	occlusion	0	0	1+	1+	0	0
3	56 F	0	0	occlusion	0	0	occlusion	0	0	0
4	59 M	0	0	occlusion	0	0	1+	1+	1+	1+
5	53 M	0	0	occlusion	0	0	0	0	2+	1+
6	67 F	0	0	occlusion	0	occlusion	0	occlusion	0	0
7	56 M	0	0	occlusion	0	0	0	1+	1+	0
8	61 M	0	0	occlusion	0	0	3+	3+	0	0
9	66 F	0	0	3+	0	0	1+	2+	2+	0
10	65 M	0	0	3+	0	0	2+	0	0	0
11	53 M	0	occlusion	0	0	0	0	0	0	1+
12	56 M	0	occlusion	0	0	0	0	0	0	0
13	60 F	0	occlusion	3+	0	0	3+	0	occlusion	0
14	44 F	0	occlusion	0	0	1+	1+	2+	0	occlusion
15	57 M	occlusion	0	3+	0	0	0?	0	0?	0

1+ = mild stenosis; 2+ = moderate stenosis; 3+ = marked stenosis.

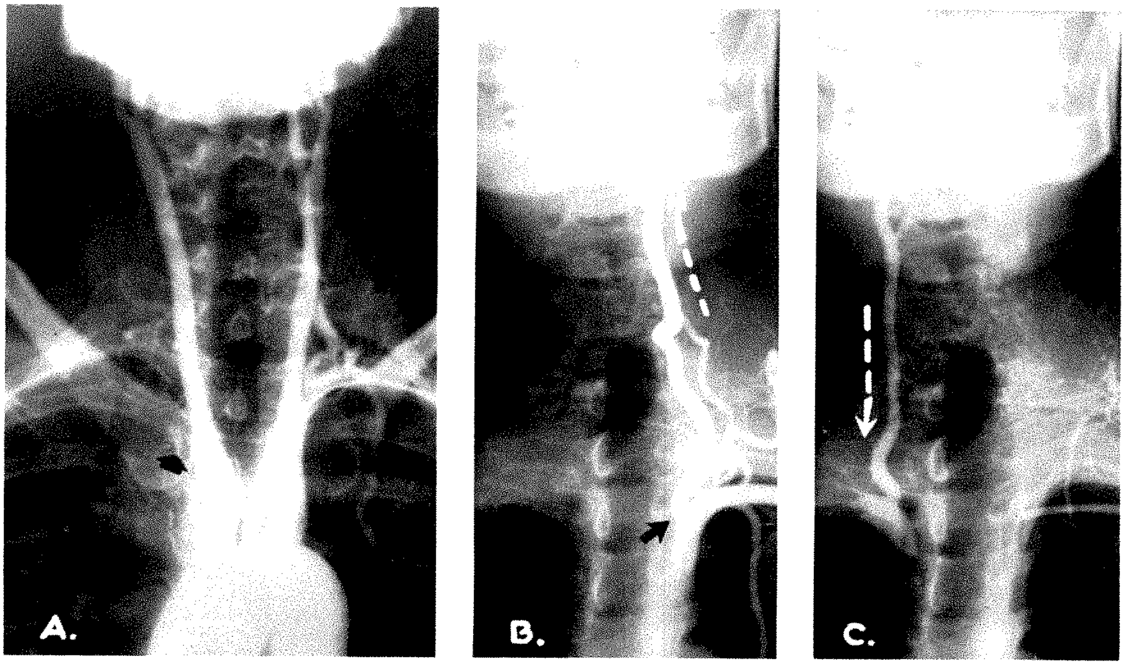

Fig. 4. (*A*, *B* and *C*) Occlusion of proximal right subclavian artery with vertebro-vertebral collateral pathway. Minimal narrowing of origin of left vertebral artery.

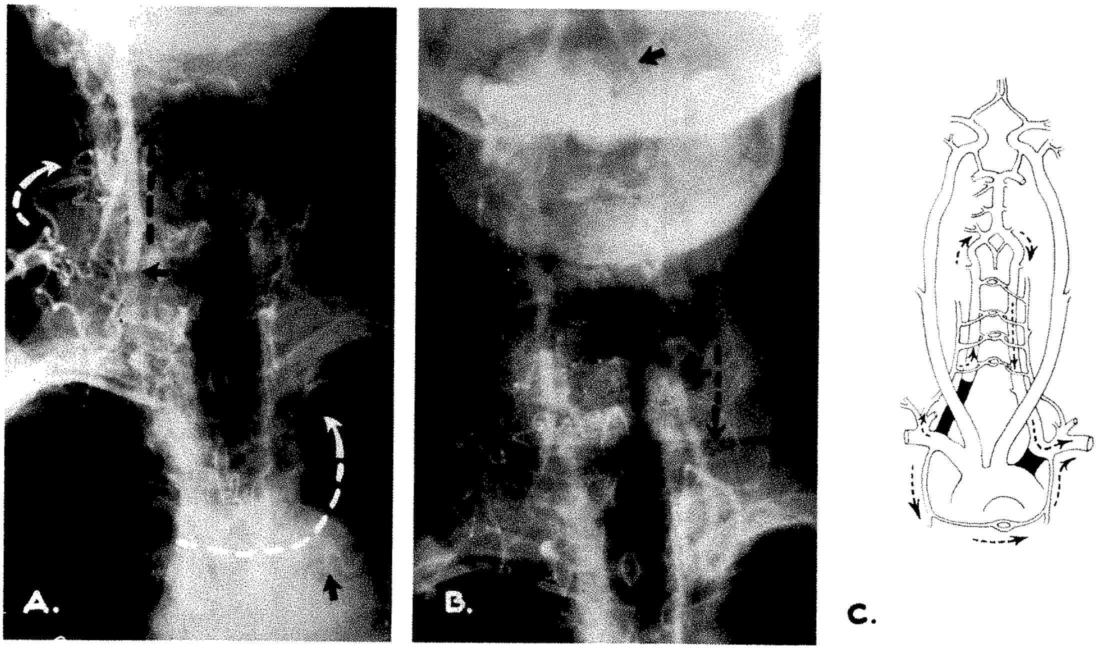

Fig. 5. (*A*, *B* and *C*) Occlusion of proximal 4 cm. of right vertebral artery. Distal right vertebral artery filled by communication with thyrocervical trunk. Vertebro-vertebral collateral pathway supplies distal left subclavian artery. (Left subclavian artery occlusion shown by aortic arch study.) Collateral connection between internal mammary arteries contributes to supply of distal left subclavian artery.

Fig. 6. Reversal of flow in left vertebral artery with failure of filling of basilar artery (proximal left subclavian occlusion).

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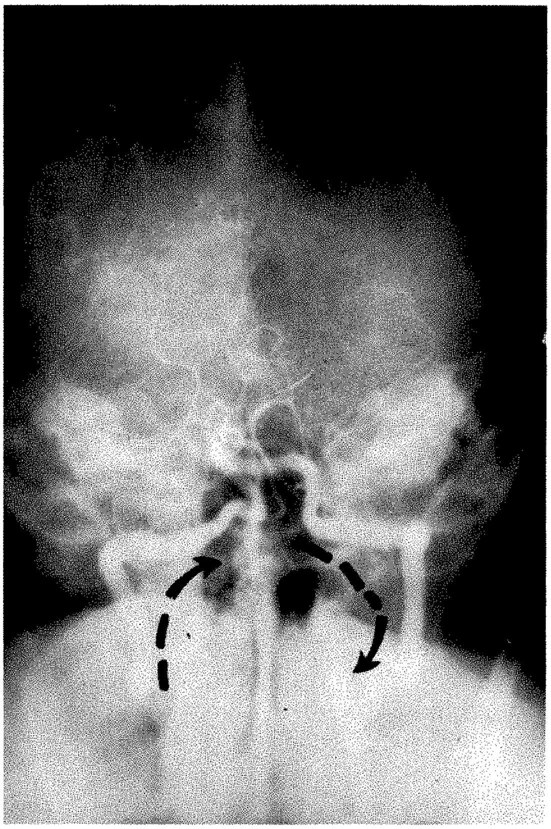

to the presence of subclavian occlusion.

c. Internal carotid-posterior communicating basilar-vertebral pathway. Theoretically, collateral blood flow arising from the circle of Willis should occur, but was not observed in our patients.*

d. Anastomosis between vertebral arteries via their muscular branches. This potential pathway, previously reported[9] was not observed in our patients.

Blood flow in a vertebral artery undoubtedly reverses when the proximal subclavian artery is used in the Blalock operation for certain forms of congenital cardiac disease. Blood flow in a vertebral artery may be reversed even though the proximal vertebral artery has been occluded surgically. In these instances, blood flowing down the vertebral artery leaves this vessel

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* See Addendum.

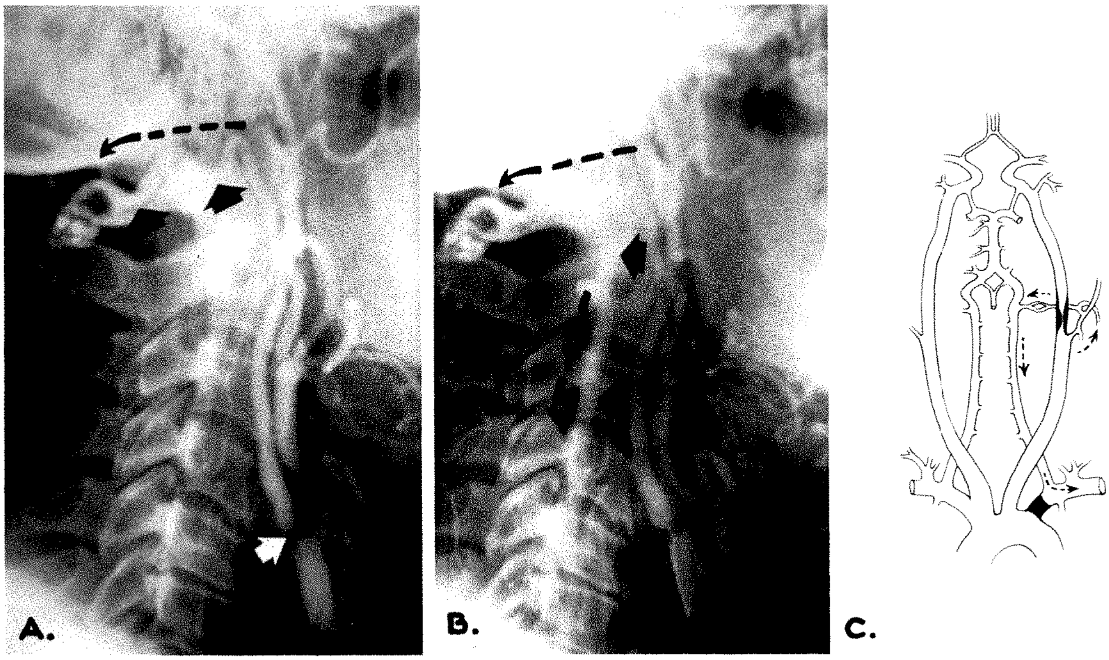

Fig. 7. (*A*, *B* and *C*) Collateral connection between occipital branches of external carotid and muscular branches of vertebral artery. Reversal of flow in vertebral artery to supply subclavian artery distal to occlusion.

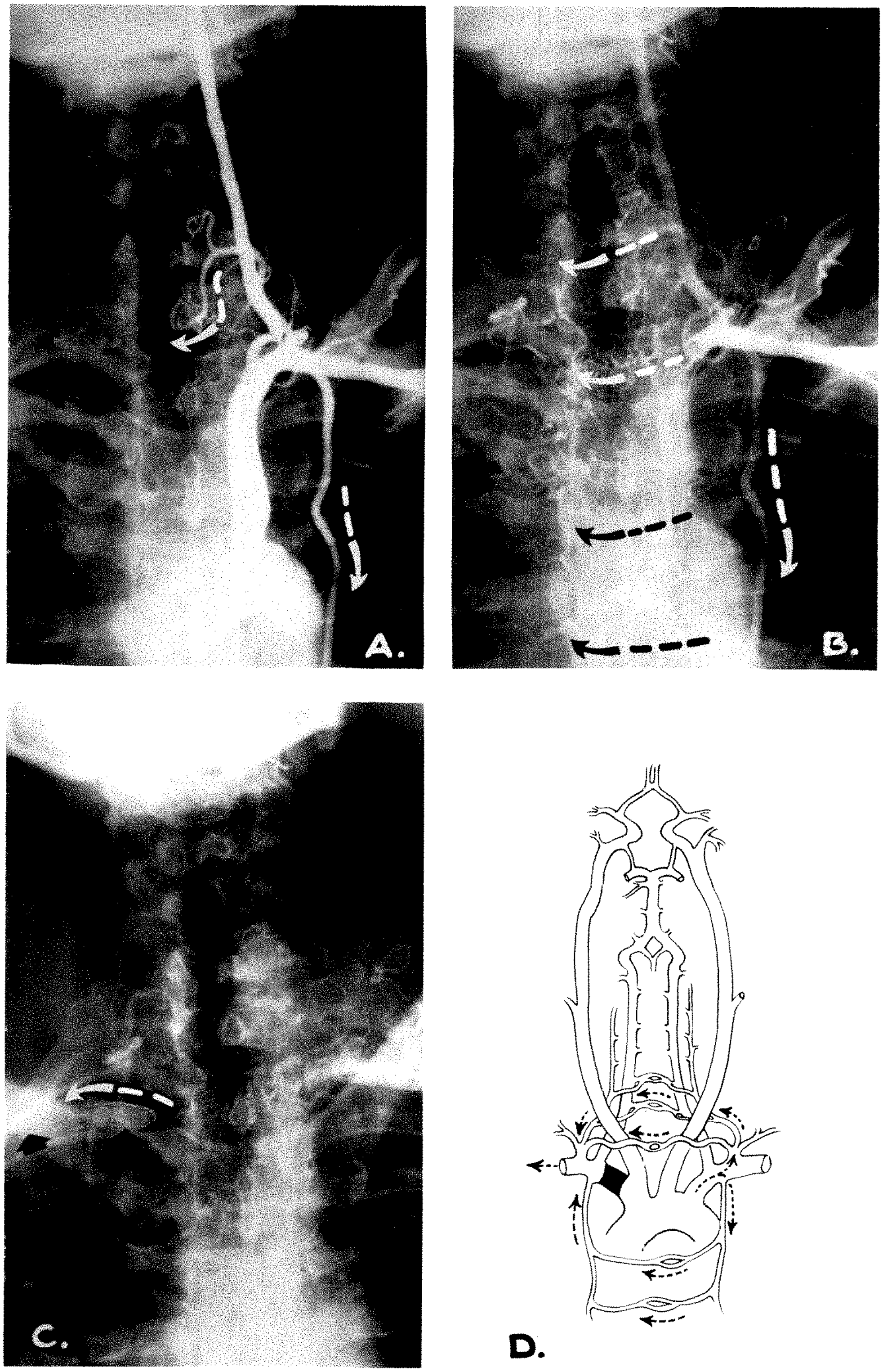

FIG. 8. (*A*, *B*, *C* and *D*) Collateral channels between thyrocervical trunks supply distal right subclavian artery. Collateral connections between internal mammary arteries also noted. (Proximal right subclavian artery occlusion.)

by way of its muscular branches. This unusual appearance was observed recently in 2 patients in whom the left vertebral artery had been occluded surgically. One had had a previous end-to-side left subclavian-aortic anastomosis to bypass an aortic coarctation. An aortic-arch study showed blood flowing down the left vertebral artery to supply the distal subclavian artery via the muscular branches of the vertebral artery. The other patient had an arteriovenous malformation in the neck. A right subclavian arteriogram showed retrograde flow down the surgically occluded vertebral artery and its muscular branches to supply the arteriovenous malformation.

In our series, other collateral routes were observed when stenosis or occlusion of the preformed vertebral collateral pathway was present.

2. ANASTOMOSIS BETWEEN THE TWO THYROCERVICAL TRUNKS VIA THE INFERIOR THYROID ARTERIES (FIG. 8, A–D)

Anastomotic channels to supply the distal subclavian artery may develop between branches of two thyrocervical trunks. Such channels were noted to a varying extent in 6 of our patients. In 1 patient these channels appeared to be the major collateral pathway to supply the distal subclavian artery (Case 14).

3. ANASTOMOSIS BETWEEN THE INTERNAL MAMMARY ARTERIES (FIG. 8, A–D; AND 9)

Collateral channels connecting the two internal mammary arteries were seen in 4 patients. In these, reversal of flow in the ipsilateral internal mammary artery supplied the distal subclavian artery. This route did not appear to be a major collateral pathway in any of our patients.

4. ANASTOMOSIS BETWEEN EXTERNAL CAROTID AND THYROCERVICAL TRUNK (FIG. 10, A, B AND C)

Collateral channels between the external carotid artery and the thyrocervical trunk may develop via the superior and inferior thyroid arteries and the ascending cervical artery. This pathway was noted in a patient with complete occlusion of the proximal right subclavian artery (Case 13). No other collateral channels arising from the contralateral side were demonstrated in this patient.

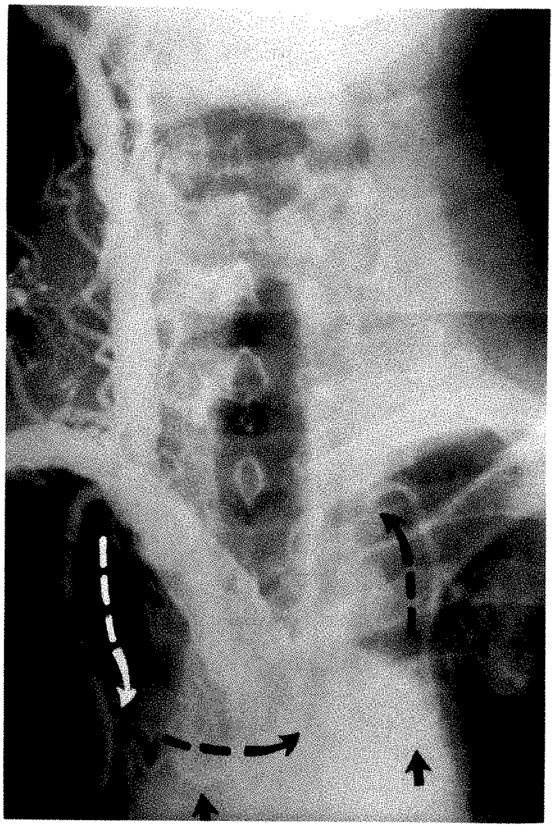

FIG. 9. Collateral connections between internal mammary arteries with reversal of flow in left internal mammary artery. (Occlusion of proximal left subclavian artery.)

5. ANASTOMOSIS BETWEEN INTERNAL CAROTID ARTERIES VIA THE CIRCLE OF WILLIS (FIG. 11, A–D)

Blood flow in the right internal and common carotid arteries supplying the right arm was reversed in 1 patient (Case 15). The innominate artery in this patient was occluded and the left subclavian artery markedly stenosed. Contrast medium injected into the left common carotid artery ascended to fill the entire intracranial circulation. Then, in a retrograde manner, the contrast medium flowed down the right common and internal carotid arteries. Reversal of flow was also observed in both

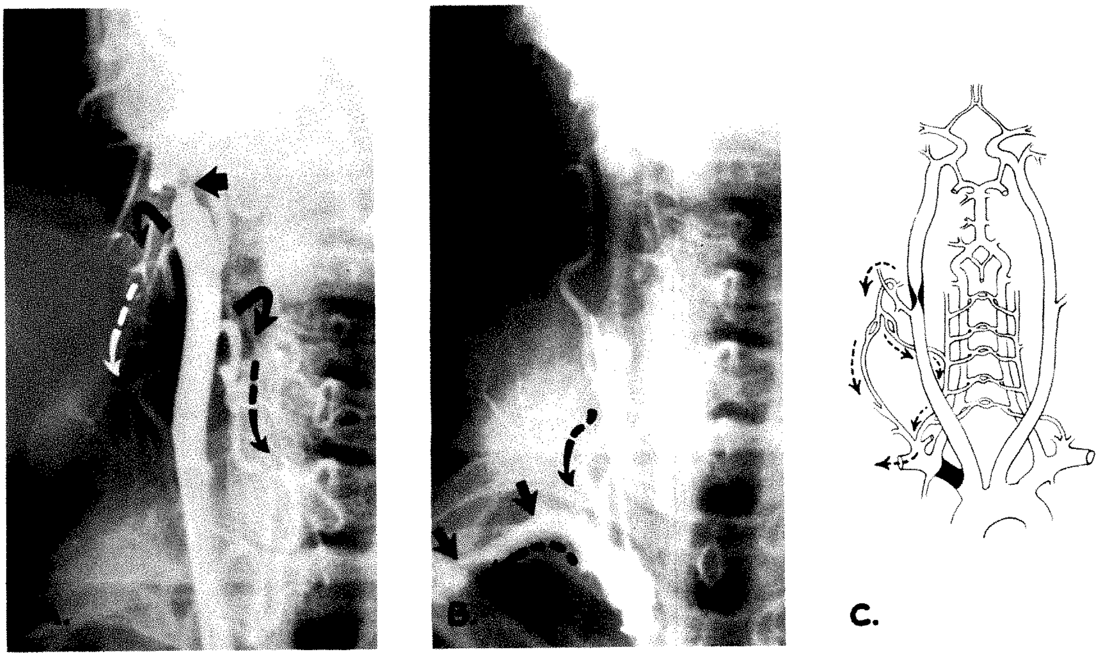

Fig. 10. (*A*, *B* and *C*) Communications between superior and inferior thyroid arteries supply distal right subclavian artery. (Occlusion of proximal right subclavian artery.)

vertebral arteries which were filled from the left internal carotid artery via the circle of Willis. Blood flow in the left vertebral artery was reversed to supply the left subclavian artery distal to the stenosis. This patient, therefore, presented an unusual phenomenon of reversed flow of blood in both vertebral and right internal and common carotid arteries. Surprisingly, the patient complained only of ischemic right upper extremity symptoms and had no neurologic difficulty.

DISCUSSION

Since the atherosclerotic process is usually well localized in the subclavian artery and thus amenable to direct surgical repair, recognition of this entity is important. Blood pressure readings of both arms in all patients with suspected cerebrovascular occlusive disease should, therefore, always be obtained. Accurate analysis of the status of the entire extracranial vascular tree is imperative since other associated arteriosclerotic lesions are common. In our experience, angiography of the aortic arch and of the brachiocephalic vessels is best approached via the percutaneous transaxillary route.[4] Serial roentgenograms are necessary to recognize late retrograde filling of the vertebral artery or other collateral pathways. Withdrawing the catheter into the uninvolved subclavian artery further facilitates demonstration of the collateral circulation to the involved subclavian artery.

SUMMARY

Occlusion or stenosis of the proximal subclavian artery in 15 patients is reported. One patient, in addition, had occlusion of the innominate artery. Several potential routes of collateral circulation to the arm are available. The most common and, also, potentially the most dangerous, is the preformed vertebro-basilar-vertebral pathway. Occlusion of the proximal subclavian artery may result in reversal of blood flow down the vertebral artery to supply the distal subclavian artery. A diversion of blood from the posterior cerebral circulation results. This syndrome, aptly called

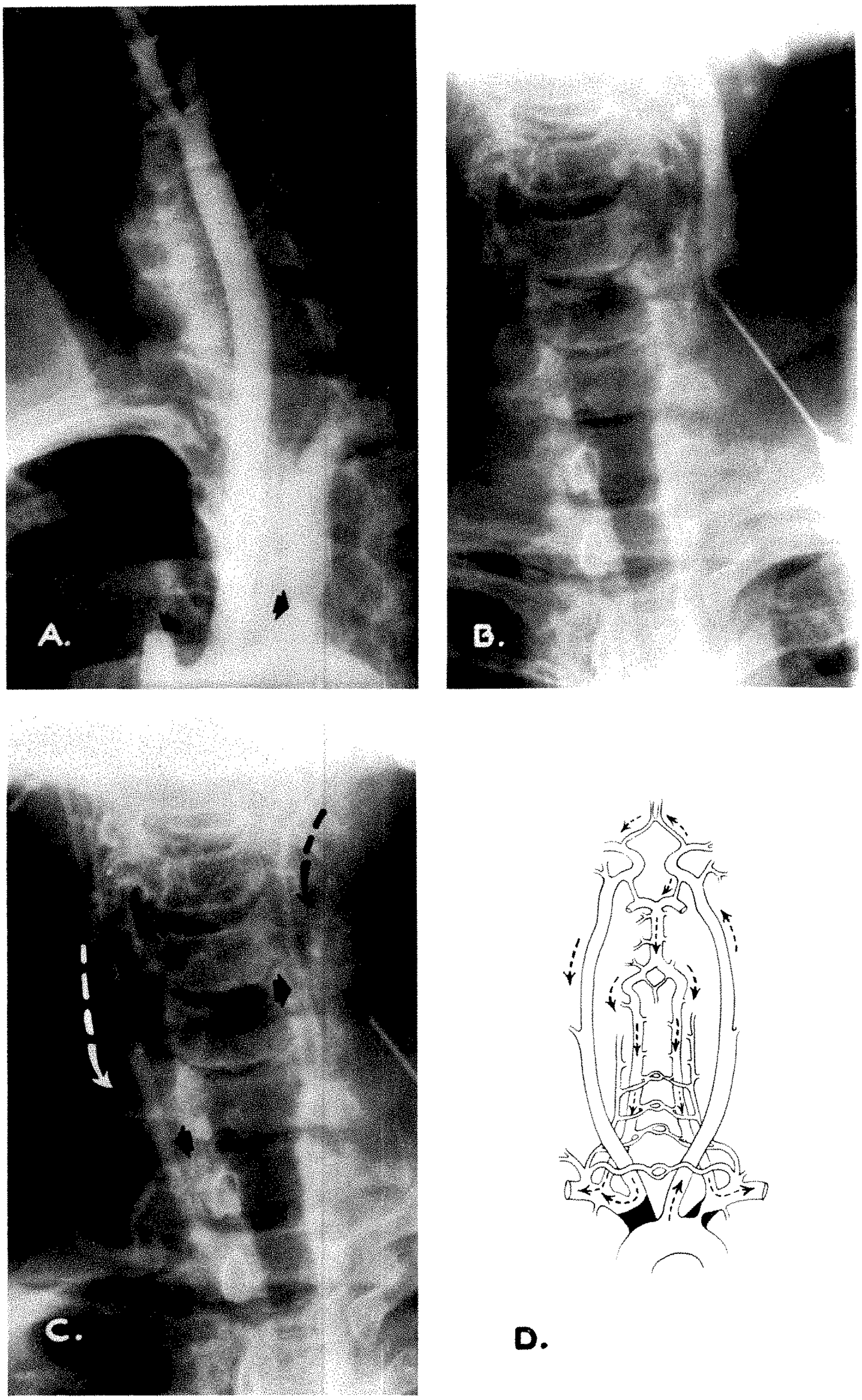

Fig. 11. (*A*) Occlusion of innominate artery with marked stenosis of left subclavian artery. (Courtesy, Dr. John C. Bennett.) (*B* and *C*) Left common carotid arteriograms. Reversal of flow in right internal and common carotid and right vertebral arteries supplies the right subclavian artery distal to innominate artery occlusion. Blood flow reversed in left vertebral artery supplies distal left subclavian artery. (*D*) Composite drawing of *A*, *B* and *C*.

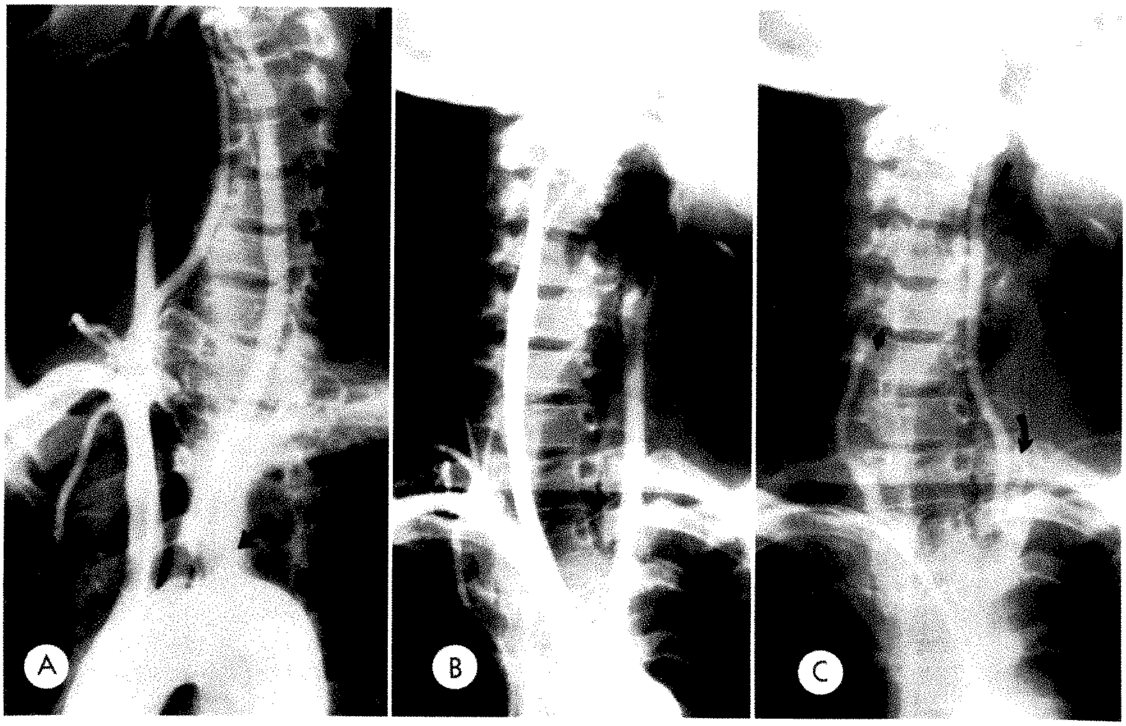

Fig. 12. (*A*) Occlusion of the proximal left subclavian artery. With the head turned toward the right, the right vertebral artery fills well. The left vertebral artery failed to fill as evidenced by delayed roentgenograms. (*B* and *C*) With the head turned to the left, the flow in the right vertebral artery is stopped in its midportion. Delayed roentgenograms show reversal of flow down the left vertebral artery by the carotid-posterior communicating basilar artery pathway. In this patient, flow in the left vertebral artery is hindered by turning the head to the right, whereas the flow in the right vertebral artery is stopped when the head is turned to the left.

the "subclavian steal" syndrome may, therefore, lead to cerebrovascular insufficiency. It should be suspected in patients with cerebrovascular insufficiency when blood pressures and pulses in the arms differ, and if a localized bruit is present. Serial angiograms of the aortic arch and its branches are needed for complete evaluation of these patients.

ADDENDUM

Since this manuscript was prepared, 11 additional patients with occlusion of the subclavian artery have been seen; 2 occlusions were on the right, 9 on the left. One of these patients demonstrated collateral pathway reaching the distal subclavian artery via the circle of Willis. Blood flowing up the internal carotid artery was diverted to the basilar artery. Blood flow was then reversed in the basilar and vertebral arteries to reach the distal subclavian artery (Fig. 12, *A–C*). In a group of 200 patients with cerebrovascular occlusive disease, complete subclavian artery occlusion was present in 22 (1 bilateral) (11 per cent), whereas vascular narrowing of more than 50 per cent was noted in 26 (13 per cent). In 32 patients (16 per cent) stenosis was of lesser degree.

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THE SUBEPENDYMAL VEINS OF THE LATERAL VENTRICLES*

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THE importance of the deep cerebral veins in cerebral angiography, specifically the internal cerebral vein and its major tributaries, has been emphasized by several authors.[3,6,9] Of the subependymal veins, the chief tributaries—the striothalamic vein and the vein of the septum pellucidum—are well known. Little attention has, however, been paid to other subependymal veins, particularly those in the walls of the atrium, the posterior and inferior horns. The only vessel of this group which has been clearly noted angiographically was described by Johanson[3] as the "vein of the posterior horn." This vessel was described previously anatomically by Browning.[1] The description by Browning of the subependymal veins of the lateral ventricles is extraordinarily complete. Unfortunately, much of the terminology that he coined is awkward and has not been generally accepted. Nevertheless, the various veins described by him and other authors[2,8] can often be identified in the venous phases of cerebral angiography and are of considerable use diagnostically. Since no arteries accompany these veins, the ability on angiography to determine the position of the ventricular walls depends on the recognition of the subependymal veins.

The striothalamic vein is the most popular name for the prominent vessel located in the striothalamic sulcus in the anterior portion of the body of the lateral ventricle. This vein runs forward, downward and medially through the posterior superior margin of the foramen of Monro to join the internal cerebral vein. The junction, in the anterior end of the velum interpositum, is shared with the vein of the septum pellucidum and the superior choroidal vein. The striothalamic vein is formed by a posterior tributary, running forward along the stria terminalis, often designated as the posterior terminal vein,[4,8] and by anterior tributaries from the surface of the head of the caudate nucleus. The anterior tributary has been designated by some authors[4,8] as the anterior terminal vein but this designation has been criticized on the basis that the stria terminalis does not extend into the frontal horn.[5] It is nevertheless convenient to have separate designations for the individual tributaries and the stem of this striothalamic system of veins. We have therefore continued to refer to the vein along the stria terminalis as the posterior terminal vein while designating anterior tributaries as anterior caudate veins. The term anterior caudate vein is also not without objection since the major anterior tributary of the striothalamic trunk often runs in the superior lateral corner of the frontal horn, a short distance above the head of the caudate nucleus. Veins running longitudinally in this corner of the frontal horn and body of the ventricle have been designated longitudinal caudate veins.[4,8] These consist of several or multiple channels to which numerous small intracerebral veins converge as a "venous fountain."[4] The longitudinal caudate vein in the frontal horn is usually a tributary of the striothalamic stem. In the body, the longitudinal caudate veins drain downward by multiple channels ("transverse caudate veins") into the posterior terminal vein or more directly into the internal cerebral vein.

In a previous report,[9] it was indicated in diagrammatic fashion that the posterior terminal vein may extend as a single continuous channel throughout the entire length of the stria terminalis, that is, from the interventricular foramen in the body of the ventricle through the atrium and down into the temporal horn. While the extent of the posterior terminal vein is variable, this vessel is usually short and rarely extends as far posteriorly as the atrium. A classification of the subependymal veins based on this vessel as the major longitudinal collecting channel is therefore not suitable. Moreover, the veins in the roof and medial wall of the lateral ventricle form an entirely separate group, totally unrelated to the stria terminalis. For purposes of a systematic classification of the subependymal veins, it is therefore simpler to consider a large posterior terminal vein as an alternative rather than as a primary or major venous channel. On this basis, local or discrete veins in each portion of the ventricular system are considered to form the basic or prototype pattern into which variations can be easily fitted.

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The subependymal veins of the lateral ventricles (Fig. 1, *A* and *B*; and 2, *A* and *B*) may be classified into two main groups, namely, a medial group and a lateral group. The use of the terms medial and lateral are not entirely self-explanatory and require some comment. Because of the bending of the lateral ventricle that occurs during development, the roof of the temporal horn is continuous with the lateral wall of the atrium and the body of the ventricle, while the floor of the temporal horn corresponds to the medial wall of the atrium and body. In cross-section (Fig. 2*B*), the temporal horn is a curved cleft with the convexity superiorly, having a roof and a floor and no significant medial or lateral walls. The roof contains in its medial portion the lamina affixa and the stria terminalis and, more laterally, the tail of the caudate nucleus and the white matter of the tapetum. The floor contains the projecting hippocampus medially and the collateral eminence laterally. The medial border of the temporal horn is formed by the choroidal fissure or the cleft between the stria terminalis above and the fimbria and the fornix below. The choroid plexus with associated pial tissue, veins and arteries passes through the cleft. The lateral border of the temporal horn is a sulcus between the roof and the collateral eminence of the floor. The posterior horn of the lateral ventricle is a late extension of the developing ventricle into the occipital lobe and the subependymal veins in the posterior horns are tributaries of adjacent atrial veins. Since the posterior horn is derived essentially from the medial wall of the embryonic lateral ventricle, almost all of the subependymal veins in this area drain into the medial group of vessels. In the radiologic literature, as in this report, the portion of the ventricle behind the thalamus and fornix is conventionally divided into atrium and posterior horn. In anatomic texts, however, the atrium is usually included in the "posterior horn."

The two groups of subependymal veins may be subdivided into those related to the frontal horn, the body, the atrium, and the inferior horn (Fig. 1, *A* and *B*). While it would be possible to refer to these veins simply as subependymal veins of each of these regions, there are vessels in each area with sufficiently characteristic appearances to be given more specific designations (Fig. 3, *A–D*; and 4, *A–D*). The medial group of subependymal veins includes: (1) in the frontal horn, the "vein of the septum pellucidum"; (2) in the body of the ventricle, posterior septal or direct medial veins; (3) in the atrium, "the medial atrial vein"; and (4) in the inferior horn, veins of the hippocampus. The lateral group includes: (1) in the frontal horn, anterior caudate veins; (2) in the body, the "direct lateral vein"; (3) in the atrium, "the lateral atrial vein"; and (4) in the inferior horn, "the inferior ventricular vein." All of these veins are not present as large channels in any given case and the borders between drainage areas are not as sharply defined as this classification might suggest.

In the frontal horn, the medial group of vessels is represented by the well known vein of the septum pellucidum. There is one such large trunk on each side of the septum pellucidum. Numerous tributaries of this vessel arise in the anterior wall and roof of the frontal horn and progressively unite to form a single trunk. The trunk runs directly backward, well above the lamina rostralis, along the line of attachment of the septum to the peduncles of the corpus callosum and septum pellucidum (Fig. 1*A*). The vein then enters the anterior end of the internal cerebral vein in conjunction with the striothalamic trunk and the supe-

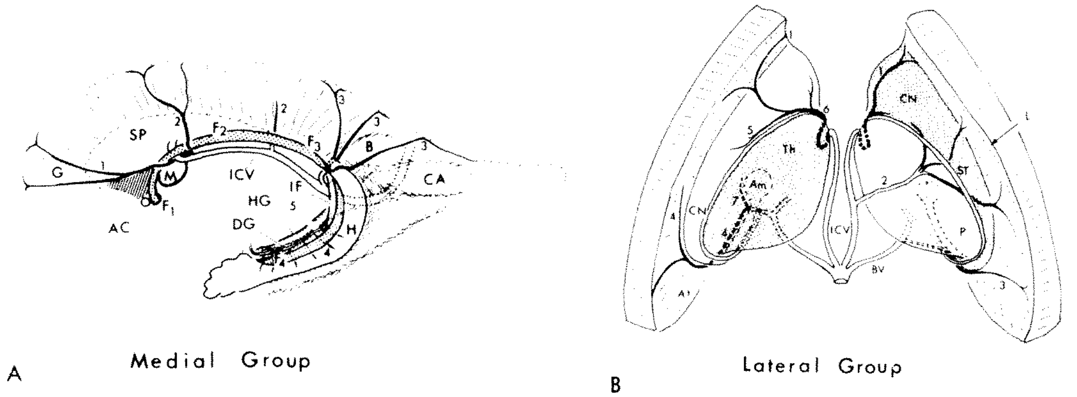


Fig. 1. Diagrammatic representation of the two groups of subependymal veins of the lateral ventricles. The intraventricular portions of these veins are drawn in solid fashion and the extraventricular unshaded.

(*A*) Medial group. The vein of the septum pellucidum (1), two posterior septal, callosal, or direct medial veins (2, 2), the medial atrial vein composed of three main tributaries (3, 3, 3), and small veins of the hippocampus (4) are illustrated. The larger and more anterior of the two septal veins runs downward lateral to the column of the fornix to join the internal cerebral vein behind the foramen of Monro. The smaller posterior septal vein runs downward between the two halves of the body of the fornix to join the internal cerebral vein. The most posterior of the tributaries of the medial atrial vein arises in the medial wall and roof of the posterior horn. The tributaries of the medial atrial vein leave the ventricle, *i.e.*, the subependymal region to enter the subarachnoid space, along the medial attached border of the fornix. A common stem is formed outside the ventricle. The multiple small transverse veins of the hippocampus leave by passing through the medial attached border of the fimbria of the fornix and join a longitudinal collecting vein (5) adjacent to the dentate gyrus. This vein is shown joining the posterior end of the internal cerebral vein or the vein of Galen. Labeled structures include the genu of the corpus callosum (G), the septum pellucidum (SP), the anterior commissure (AC), the interventricular foramen (M), the four portions of the fornix (shaded)—column (F_1), body (F_2), posterior pillar (F_3), and fimbria (F_4), the internal cerebral vein (ICV), the bulb in the atrium and posterior horn (B), the calcar avis (CA), the hippocampus (H), the dentate gyrus (DG), the hippocampal gyrus (HG), and the inferior fasciculus of the forceps major (IF). The inferior fasciculus includes those fibers of the forceps major extending from the lower inferior portion of the splenium to the lingual gyrus. The hatched triangular area below the stem of the vein of the septum pellucidum lies between the lamina rostralis of the genu and the column of the fornix. It is composed of the so-called peduncles of the corpus callosum and septum pellucidum and the septum *per se* is attached along its upper margin.

(*B*) Lateral group. The medial wall and the roof of all portions of the lateral ventricles have been removed. The structures remaining are shown as viewed from behind and above. The caudate and amygdaloid nuclei are shaded on the right; the thalamus is shaded on the left. On the right side, three veins of the lateral group are shown—an anterior caudate vein (1), the direct lateral vein (2), and the lateral atrial vein (3). On the left side, the anterior caudate vein (1) runs above the head of the caudate nucleus and joins the posterior terminal vein (5) to form the striothalamic stem (6). On this side, a large inferior ventricular vein (4, 4) is shown arising along the upper or lateral border of the tail of the caudate nucleus and extending into the temporal horn. This vein receives small twigs from the tip of the temporal horn (7) as it turns medially to enter the basal vein. Note that all the veins of the lateral group run deep to the stria terminalis. Labeled structures include the caudate nucleus (CN), the stria terminalis (ST), the pulvinar of the thalamus (P), the thalamus (Th), the amygdaloid nucleus (Am), the lateral wall of the atrium (At), the basal vein (BV), the internal cerebral vein (ICV), and the superior lateral corner of the body of the ventricle (L).

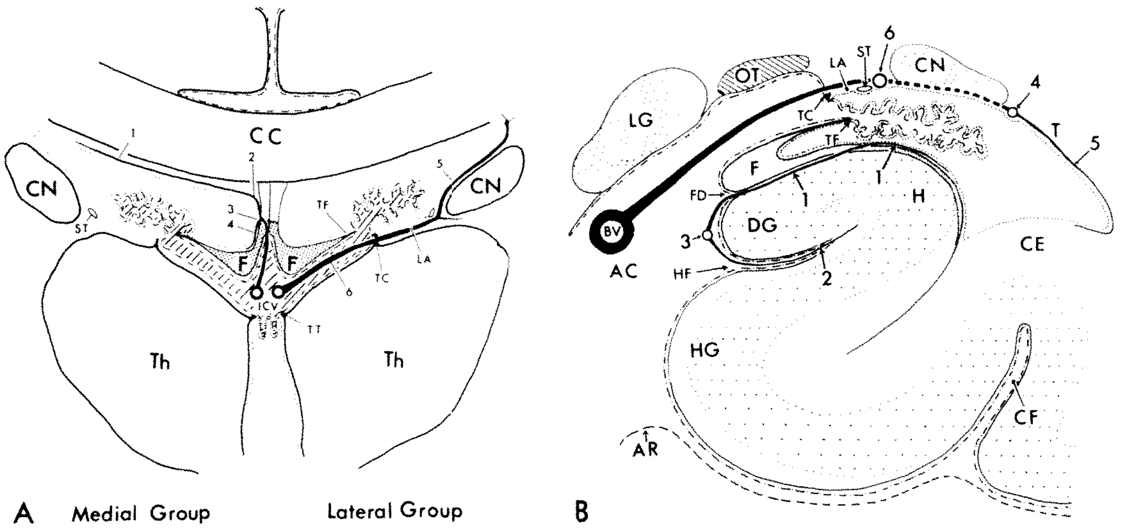


FIG. 2. Coronal cross-sections to indicate the different modes of exit of the medial and lateral subependymal veins.

(*A*) Section through the posterior portion of the bodies of the lateral ventricles. The velum interpositum (hatched) intervenes between the fornix (shaded) and the thalamus on each side and continues laterally through the choroidal fissure into the choroid plexus of the lateral ventricle. Labeled structures include the thalamus (Th), the body of the fornix (F), the caudate nucleus (CN), the stria terminalis (ST), the lamina affixa (LA), the tenia thalami (TT), the tenia of the fornix (TF), the corpus callosum (CC), and the internal cerebral vein (ICV). On the reader's left, a posterior septal or direct medial vein is shown beginning in the roof (1) of the ventricle, turning down in the septum pellucidum (2), and perforating (3) the fused portions of the two halves of the body of the fornix. The vein then enters the velum interpositum and runs directly downward into the internal cerebral vein. A small twig (4) from the fornix runs upward to join this vein at the upper margin of the fornix. On the reader's right, a direct lateral vein (6) is illustrated. This vessel is shown as continuous with a transverse caudate vein (5) beginning in the superior lateral corner of the ventricle. The vein then runs medially underneath the stria terminalis, the lamina affixa, and the tenia choroidea to enter the velum interpositum and continues over the thalamus to reach the internal cerebral vein.

(*B*) Section through the inferior horn behind the amygdaloid nucleus and uncus. Labeled structures include the tapetum (T), the caudate nucleus (CN), the stria terminalis (ST), the lamina affixa (LA), the optic tract (OT), the lateral geniculate body (LG), the tenia choroidea (TC), the tenia fimbria (TF), the fornix (F), the hippocampus (H), the dentate gyrus (DG), the fimbriodentate sulcus (FD), the hippocampal fissure (HF), the hippocampal gyrus (HG), the wing of the ambient cistern (AC), the collateral eminence (CE), the collateral fissure (CF), the basal vein (BV), and the arachnoidal reflection (AR) from the hippocampal gyrus. A small transverse subependymal vein (1, 1) on the hippocampus runs medially below and through the attached portion of the fornix to leave the ventricle and appear in the fimbriodentate sulcus. A small pial vein (2) arises deep in the hippocampal fissure. These veins join a longitudinal hippocampal vein (3) adjacent to the dentate gyrus. The inferior ventricular vein (4) is shown in cross-section as it runs forward in the roof of the temporal horn lateral to the caudate nucleus. A tributary (5) arising in the lateral corner of the inferior horn extends medially in the roof to join this vein. When the inferior ventricular vein reaches a plane anterior to this section, it loops medially and backward and therefore appears a second time (6) in this section. The looped anterior portion of this vessel is indicated in dashed fashion (between 4 and 6). This vessel leaves the ventricle deep to the stria terminalis, lamina affixa, and tenia choroidea to join the basal vein. Note that the mode of exit of the transverse hippocampus veins is similar to that of the direct medial vein of the body while the inferior ventricular vein resembles the direct lateral vein.

rior choroidal vein. As this vein approaches this junction, it runs lateral to the anterior pillar or column of the fornix. In addition to this major vessel, there are other small veins or veinlets deeper in the septum pellucidum which may run medial to the column of the fornix to enter the internal cerebral vein independently of the major

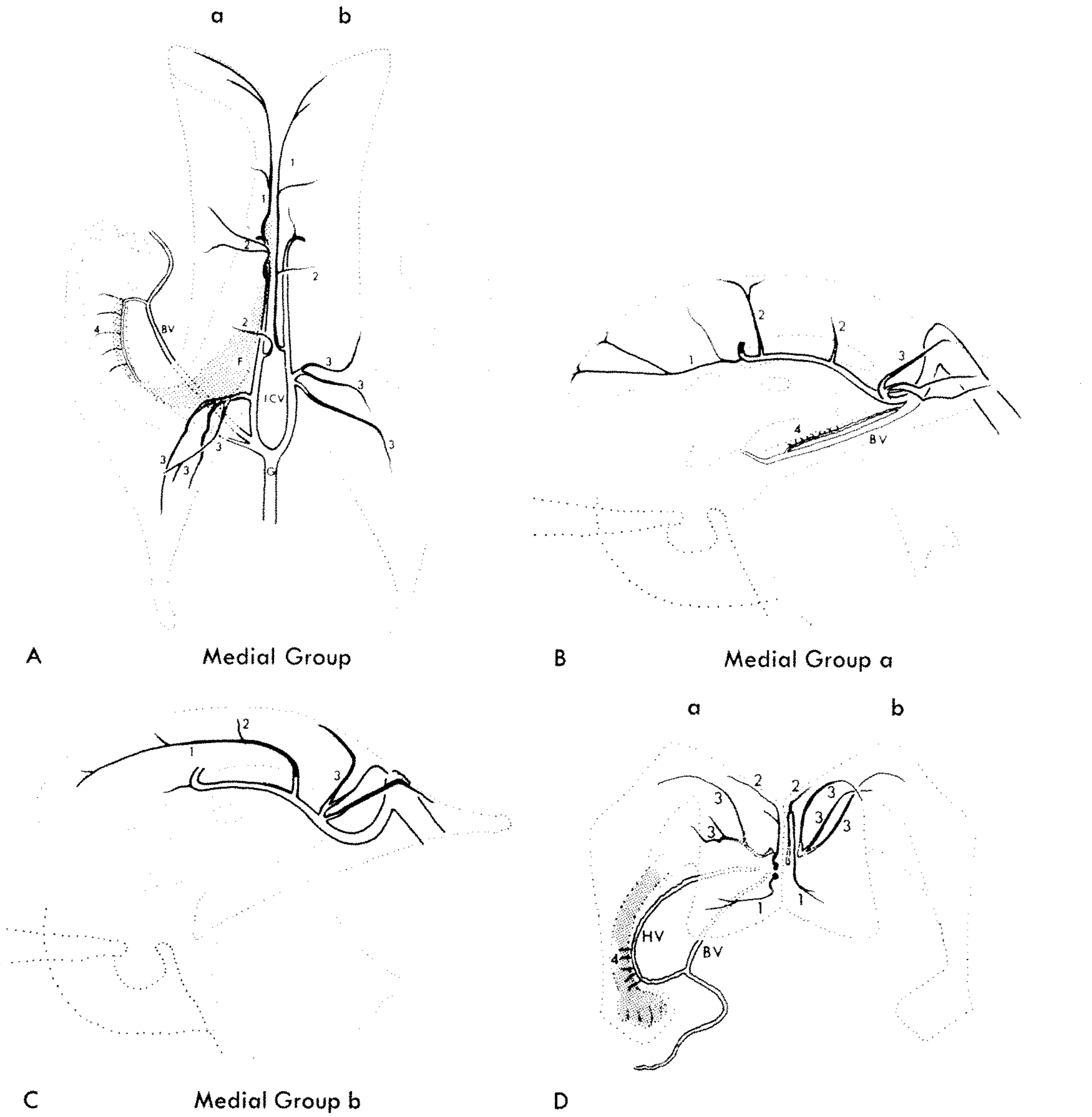


Fig. 3. Idealized appearance of the medial group of subependymal veins as they might be seen on an angiogram. The intraventricular portions are drawn in solid fashion and the extraventricular unshaded.

(*A*) Base view. Two different arrangements are illustrated (a and b). In a, the fornix (F) is shaded. On this side, the typical appearances of the vein of the septum pellucidum (1), posterior septal or callosal veins (2,2), medial atrial tributaries from the roof and medial wall of the atrium and posterior horn (3,3,3), and veins of the hippocampus (4) are shown. The veins of the hippocampus join the extraventricular longitudinal hippocampal vein along the dentate gyrus. The usual course of the basal vein (BV) is also indicated. In b, a long anomalous vein of the septum pellucidum (1) is illustrated entering the posterior portion of the internal cerebral vein. A small posterior septal vein (2) joins the main septal vessel. On this side, the tributaries (3,3,3) making up the medial atrial vein are shown as draining a larger area, including a portion of the body of the ventricle. The internal cerebral vein (ICV) and the vein of Galen (G) are also labeled.

(*B*) Lateral view of arrangement a of the medial group of subependymal veins. The same vessels shown in the base view are illustrated in this projection. The small transverse hippocampal veins (4) are seen almost on end. The longitudinal hippocampal vein is shown as joining the basal vein (BV) both anteriorly and posteriorly.

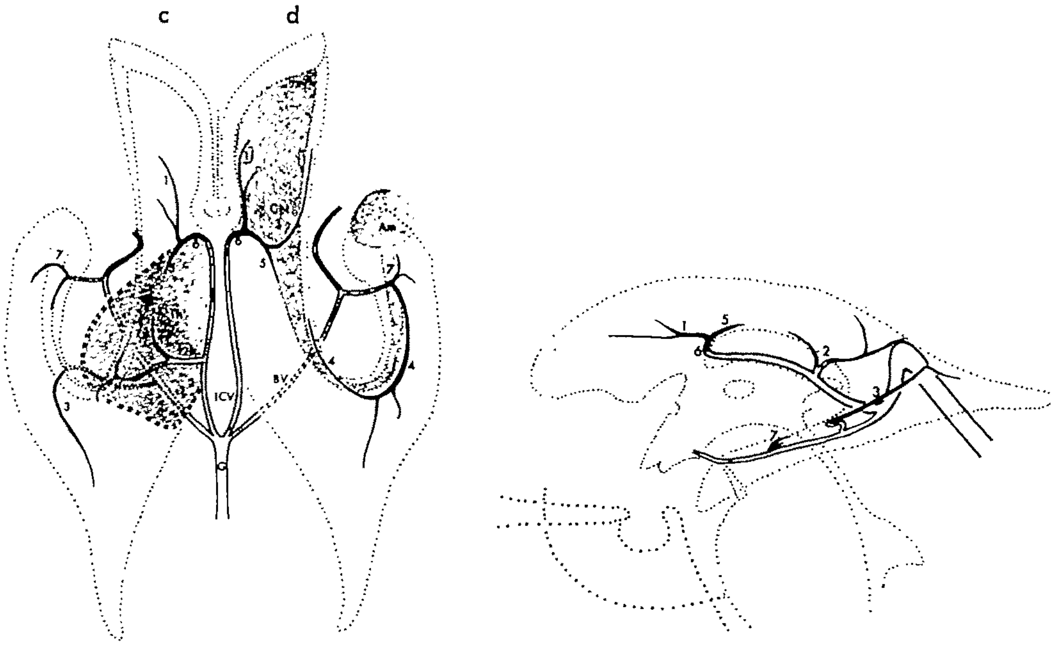
vein of the septum pellucidum. In the terminology of Browning, these small veinlets were designated as true septal veins, while the vein of the septum pellucidum was designated by this author as the anterior ventricular vein. While these names may have greater validity, it would seem desirable to continue to use the term "vein of the septum pellucidum" in its current sense since the veinlets within the septum are not important angiographically. It is nevertheless of interest that there are two groups of veins in the septum pellucidum, one immediately subependymal on the ventricular side and a second, more deeply located, in the septum pellucidum, and to note that these vessels enter the velum interpositum in a different fashion in relationship to the column of the fornix. The deep veinlets drain the septum itself while the vein of the septum pellucidum drains a large portion of the frontal pole of the cerebral hemisphere. The angiographic appearance of the septal vein has been previously described in detail.[3,6,9] It might be noted, however, that this vein often enters the internal cerebral vein posterior to the foramen of Monro and that it may run for a considerable distance below or sometimes (Fig. 3, *A–D* and 5, *A* and *B*) well above the level of the internal cerebral vein. A vein of this latter type joining the posterior portion of the internal cerebral vein from above enters the velum interpositum between the two halves of the body of the fornix.

The medial group of veins in the body of the ventricle originate in the roof, run medially and then downward in the rapidly diminishing septum pellucidum behind the interventricular foramen. These veins are usually small (Fig. 6*A*) and correspond in their septal course to the deep twigs or veinlets in the anterior portion of the septum pellucidum, that is, they run between the two halves of the fornix to enter the velum interpositum. There may, however, be a relatively large septal vein (Fig. 6*B*) a short distance behind the foramen of Monro which enters the internal cerebral vein by running lateral to the junction of the column and body of the fornix. The medial group of veins in the body of the ventricle have no generally recognized specific name. Browning referred to these vessels as "anterior and posterior internal callosal veins" since their drainage area appears to consist primarily of adjacent portions of the corpus callosum. They might be designated "posterior septal veins" in contrast to the more anteriorly located vein of the septum pellucidum. Since these vessels run essentially in the frontal plane, they might also be designated "direct medial veins" corresponding in terminology to the "direct lateral vein" to be described below.

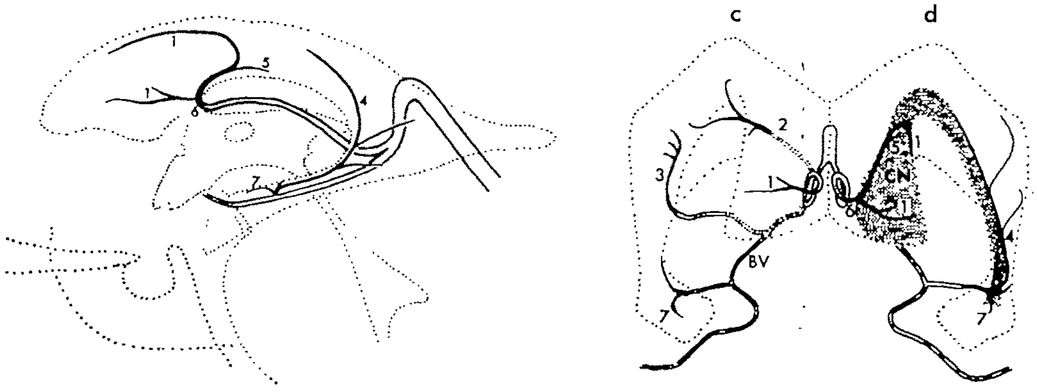
The medial wall of the atrium usually shows a prominent vein formed by several tributaries (Fig. 7, *A* and *B*; 8, *A* and *B*; and 9, *A* and *B*). The most anterior of these tributaries often arises in the roof of the posterior portion of the body of the ventricle while the most posterior tributary originates in the medial wall or roof of the posterior horn. These tributaries form a

(*C*) Lateral view of arrangement b. The anomalous vein of the septum pellucidum (1) has a striking appearance in this projection. The anterior tributary of the medial atrial vein (3) arises in the roof of the posterior portion of the body of the ventricle.

(*D*) Anteroposterior view of the two sides. In a, the hippocampus is shaded and the longitudinal hippocampal vein (HV) and basal vein (BV) are indicated. The internal cerebral vein and the vein of Galen (not drawn) ordinarily obscure the central portions of the veins of the septum pellucidum (1,1) and posterior septal veins (2,2). The medial atrial venous tributaries (3) shown in a, begin more posteriorly than those shown in b, and therefore differ somewhat in appearance.



A Lateral Group B Lateral Group c



C Lateral Group d D

FIG. 4. Idealized angiographic appearance of the lateral group of subependymal veins. The intraventricular portions of the veins are solid, the extraventricular unshaded.

(*A*) Base view. Two different arrangements (c and d) are shown. In c, the thalamus is shaded. On this side, a small anterior caudate vein (1), a direct lateral vein (2), a lateral atrial vein (3), and small twigs (7) from the roof of the tip of the temporal horn are shown. A small posterior terminal vein (5) joins the anterior caudate vein near the foramen of Monro to form a short striothalamic stem (6). In d, the caudate nucleus and the amygdaloid nucleus are shaded. On this side, two anterior caudate veins (1,1) are shown. The more medial of these veins is located on the lower aspect of the head of the caudate nucleus. The more lateral lies superiorly above the caudate nucleus. The latter vein joins the posterior terminal vein (5) in the floor of the lateral ventricle to form a relatively long striothalamic stem (6) which receives the other caudate vein near the foramen. A large inferior ventricular vein (4, 4) is shown running lateral to the caudate nucleus into the temporal horn. This vessel receives the small temporal tip veins (7) as it turns medially through the anterior end of the choroidal fissure to enter the basal vein. Labeled structures include the caudate nucleus (CN), the amygdaloid nucleus (Am), the thalamus (Th), the basal vein (BV), the internal cerebral vein (ICV) and the vein of Galen (G).

(*B*) Lateral view of arrangement c, showing the same vessels—anterior caudate vein (1), posterior

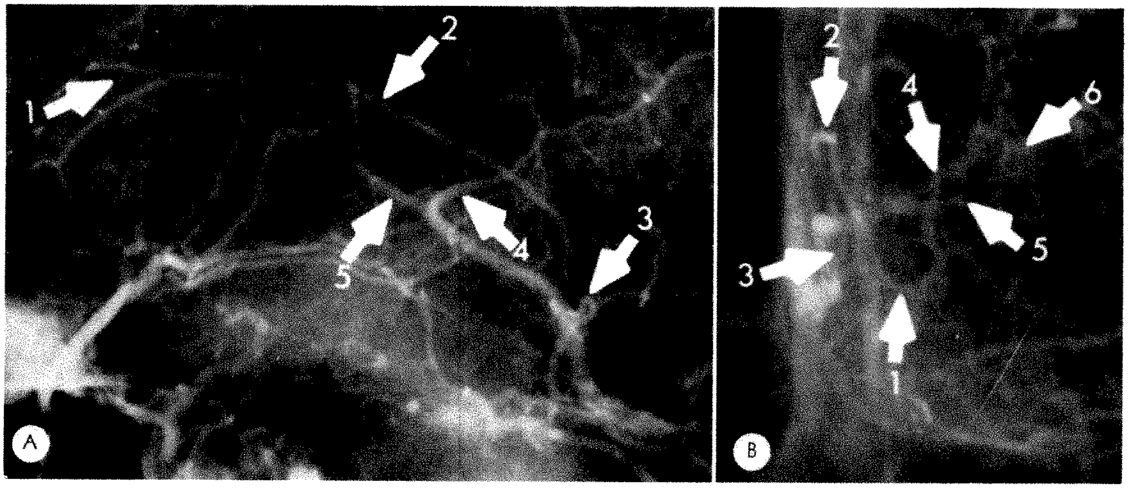


Fig. 5. Anomalous vein of the septum pellucidum.

(*A*) Lateral projection. The vein of the septum pellucidum begins in its characteristic location by the union of several tributaries from the anterior wall of the frontal horn (1), extends backward in an arcuate configuration with convexity superiorly (2), and joins the internal cerebral vein posteriorly (3). There is a large striothalamic vein (4) which joins the internal cerebral vein at about its mid-portion well behind the foramen of Monro. In this view, the anterior caudate vein (5) appears to be in line with the internal cerebral vein but is actually more laterally located.

(*B*) Anteroposterior projection shows overlapping superficial veins. However, because of the slight obliquity, the anomalous vein of the septum pellucidum (arrows 1,2,3) can be seen and has a hairpin configuration. It begins anteriorly (1), and runs up and then down (2) to join the posterior portion of the internal cerebral vein (3). The striothalamic vein (4) and the anterior caudate vein (5) join to form a short transverse striothalamic stem which runs medially to the internal cerebral vein. A horizontal course of this type is typical of the striothalamic vein when it enters the internal cerebral vein behind the foramen of Monro. Several small longitudinal caudate veins (6) outline the superior lateral corner of the frontal horn.

converging pattern and unite into a short common stem which runs transversely to join the posterior end of the internal cerebral vein. The various tributaries form a series of vessels which perforate the thin wall of the ventricle along the medial aspect of the body and posterior pillar of the fornix (Fig. 10) and form a common stem below the splenium. In the lateral projection, the anterior tributary of this vein runs downward and backward, the middle tributary almost vertically, and the posterior tributary downward and forward. The posterior tributary often has a

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terminal vein (5), striothalamic stem (6), direct lateral vein (2), lateral atrial vein (3) and temporal tip twigs (7).

(*C*) Lateral view of arrangement d. The two anterior caudate veins (1,1), posterior terminal vein (5), striothalamic vein (6), inferior ventricular vein (4) and temporal tip twigs (7) are indicated. The superior of the two caudate veins may be considered to be part of the longitudinal caudate system.

(*D*) Anteroposterior view of the two arrangements of the lateral group of veins. In d, the caudate nucleus (CN) is shaded. In c, the anterior caudate vein (1), the direct lateral vein (2), the lateral atrial vein (3), and the tip twigs (7) are shown. In d, the two anterior caudate veins (1,1) can be seen to have a rather marked difference in appearance. The terminal vein (5) arises posteriorly in the striothalamic sulcus. The large inferior ventricular vein (4) has a typical course. The tip veins on this side (7) join the inferior ventricular vein.

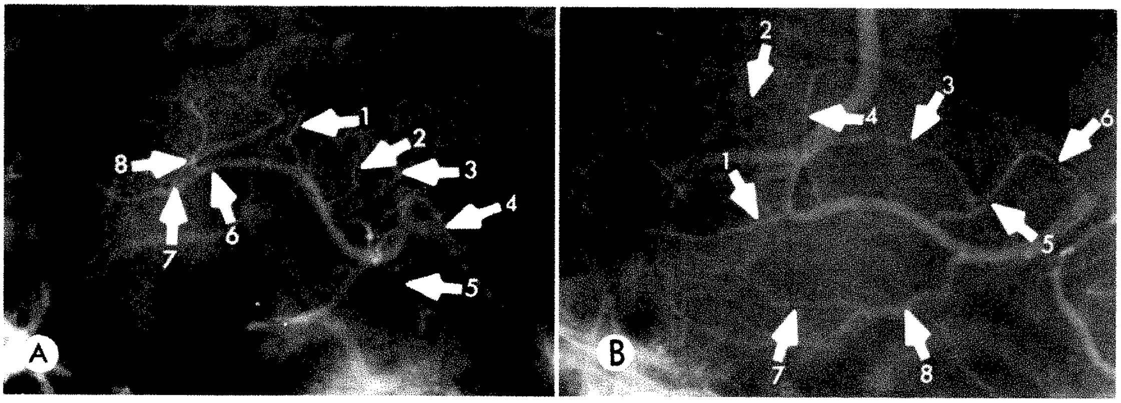

Fig. 6. Posterior septal veins.

(*A*) Lateral projection. Several small posterior septal veins (1,2,3) run downward to enter the posterior portion of the internal cerebral vein. The most posterior of these (3) might also be considered to belong to the medial atrial group of veins. A large vein from the posterior horn (4) is in line with this series of vessels. Several veins belonging to the lateral group of subependymal veins are also seen. Small twigs (5) form a lateral atrial vein which runs downward and forward to join the basal vein. The anterior caudate vein enters (6) the internal cerebral vein independently of and behind the entrance (7) of the posterior terminal vein. At the apparent point of crossing of the caudate and terminal veins (8), the posterior terminal vein is located in the floor of the ventricle while the caudate vein is near the mid-line. The vein of the septum pellucidum joins the posterior terminal vein in typical fashion (7).

(*B*) Lateral projection. Patient with a moderate degree of hydrocephalus. The tributaries and the main stem (1) of the vein of the septum pellucidum show a typical but somewhat stretched appearance. The anterior caudate vein (2) arises above the caudate head and unites with a long posterior terminal tributary (3) to form a typical striothalamic stem. A large posterior septal vein (4) runs directly downward to join the internal cerebral vein a short distance posterior to its origin. There is also a prominent medial atrial vein (5) with a characteristic tributary from the posterior horn (6). A horizontal vein (7), possibly from the thalamus, runs posteriorly to join the basal vein (8).

very characteristic configuration. It begins in the posterior horn and runs upward and forward in a rather straight course corresponding to the roof of the posterior horn. It then turns sharply downward at the junction of the posterior horn with the atrium. This angulation is quite constant and useful diagnostically. When there is a single large tributary from the posterior horn, it can conveniently be designated as the vein of the posterior horn. The vein designated by Johanson[3] as "the vein of the posterior horn" includes not only this vessel but the other tributaries of the medial atrial vein as well. In the anteroposterior projection (Fig. 7*B*, 8*B* and 9*B*), the tributary from the posterior horn also has a characteristic appearance. It begins posteriorly at some distance from the mid-line and extends toward the mid-line with a typical curved course convexity directed medially and superiorly. The more anterior tributaries of the medial atrial vein in this projection show a more horizontal course and more acute angulation as they turn downward toward the mid-line. The number and size of the tributaries of the medial atrial vein are variable. Occasionally, several small veins (Fig. 11, *A* and *B*) running more or less horizontally forward to join the posterior end of the internal cerebral vein are present. In other instances, the vessel may be quite large and, in the presence of hydrocephalus, may have a very striking appearance (Fig. 9, *A* and *B*).

The veins in the floor of the temporal horn rarely form a single large trunk. They are represented by numerous small veins on the surface of the hippocampus (Fig. 10; and 11, *A* and *B*) which run transversely underneath the fimbria of the fornix to appear outside the ventricle on the dentate gyrus. A small longitudinal

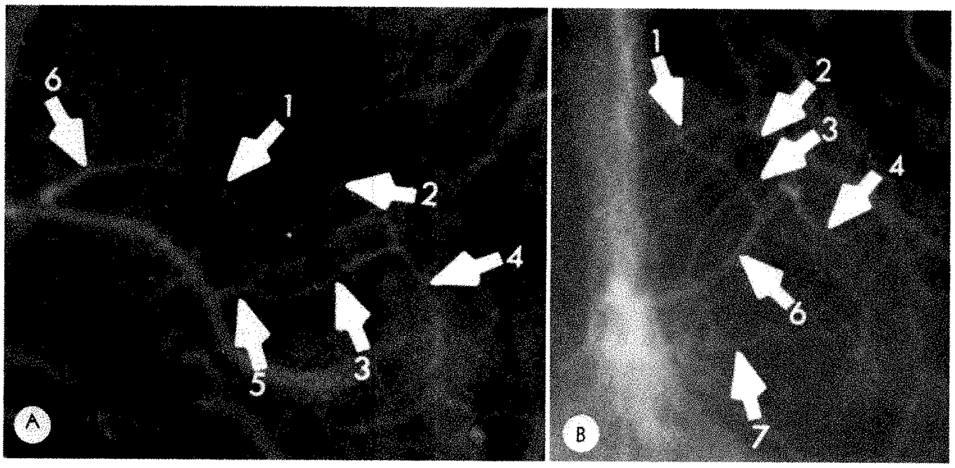

Fig. 7. Typical medial atrial vein.

(*A*) Lateral projection. Three main tributaries (1,2,3) unite to form a short stem (5) which joins the internal cerebral vein near its junction with the great vein of Galen. The anterior tributary (1) arises in the roof of the body of the lateral ventricle. The central tributary (2) arises in the roof of the atrium. The posterior tributary (3) on the medial wall of the atrium also drains a vein from the posterior horn (4). Typical anterior caudate and posterior terminal veins unite (6) to form a striothalamic stem.

(*B*) In the anteroposterior projection, the tributaries of the medial atrial vein (1,2,3) form a continuous series. The most posterior (3) begins in the posterior horn (4) and shows a typical arcuate course with convexity medially as it runs toward the mid-line. A short distance medial to this tributary, the middle branch (2) can be faintly seen and, just medial to this is the anterior branch (1). The largest vessel in this projection is the striothalamic vein (6). A transverse vein (7) joining the vein of Galen posteriorly is an external or superficial medial occipital (calcarine) vein. This vessel can be seen only faintly in the lateral projection.

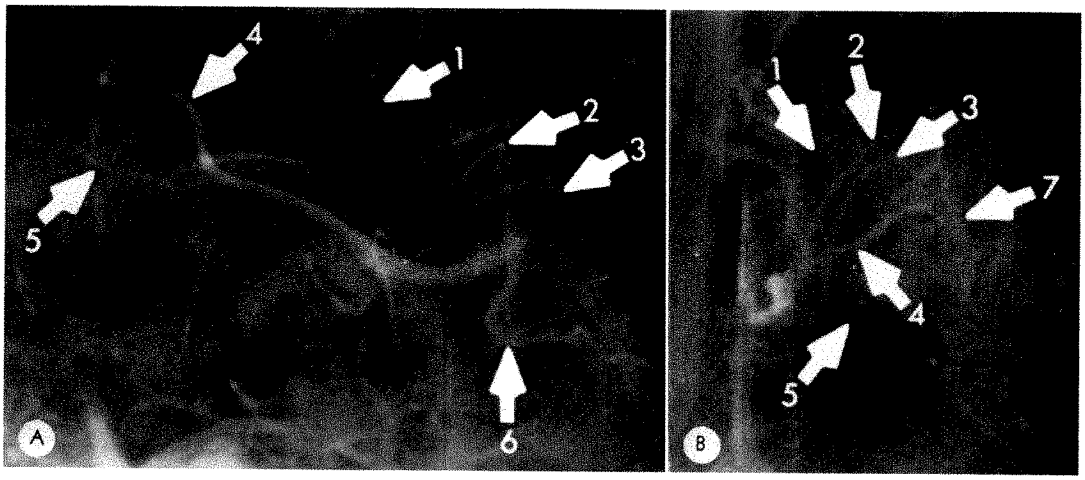

Fig. 8. Typical medial atrial veins.

(*A*) Lateral projection. Three main tributaries or medial atrial veins begin in the roof of the body (1), of the atrium (2), and posterior horn (3). These veins appear to join the posterior end of the internal cerebral vein independently. A prominent anterior caudate vein (4) runs backward and downward over the head of the caudate nucleus and joins the internal cerebral vein behind and independently of the posterior terminal vein. The septal vein (5) is small. The tortuous vessel (6) joining the posterior end of the great vein of Galen is a superficial vein in the calcarine fissure.

(*B*) In the anteroposterior projection, the three medial atrial veins (arrows 1,2,3) form a continuous series. The most anterior is also the most medial while the most posterior is the most lateral. The prominent anterior caudate vein (4) receives several tributaries from the longitudinal caudate veins (7). The septal vein (5) can be faintly seen.

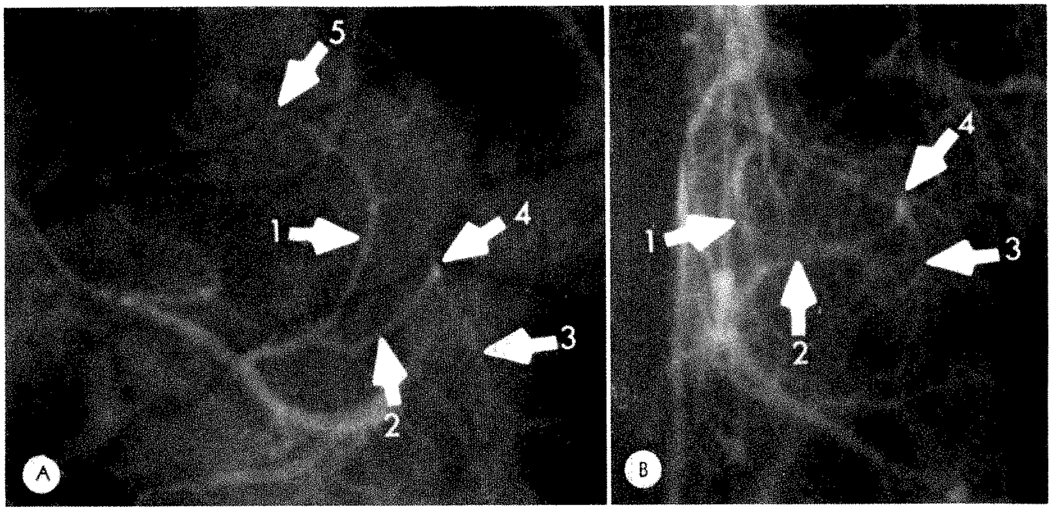

FIG. 9. A very prominent medial atrial vein in a patient with marked hydrocephalus.

(*A*) Lateral projection. The medial atrial vein is formed by two large tributaries, one anterior (1) ar one posterior (2). The posterior tributary begins in the posterior horn (3) and then bends acutely dow ward and forward (4) at the junction of the posterior horn with the atrium. The anterior tributary begi rather far forward in the roof of the body of the ventricle (5). The over-all stretching of these vess is obvious. The striothalamic vein receives a long anterior caudate vein.

(*B*) In the anteroposterior projection, the vein of the posterior horn (3) extends upward along t medial wall to the roof (4). At this point, this tributary turns and runs medially to the mid-line in t roof and medial wall of the atrium (2). The large anterior tributary is clearly seen only in its posteri downward course (1). This vein lies close to the mid-line and is evident only because of slight rotation the head.

collecting vein is present adjacent and parallel to the course of the dentate gyrus which may join the basal vein anteriorly or, more commonly, extend posteriorly to join the internal cerebral or basal vein. This longitudinal collecting vessel also receives small tributaries from the substance of the hippocampus,[2] from the uncus, and the hippocampal gyrus, that is, from the "hippocampal formation." These veins as a group may be referred to as the hippocampal venous formation. Many of the small transverse tributaries join the longitudinal trunk at a right angle simulating the appearance of a rake. This rake appearance of the venous pattern has also been noted within the substance of the hippocampus.[7] Angiographically, because of the small size of these vessels, they are rarely seen as discrete trunks. Occasionally, however, portions of the hippocampal venous formation can be identified. In a rare instance, the vein paralleling the course of the dentate gyrus may be extrao dinarily large and appears to replace t normal basal vein (Fig. 10; and 12, *A* an *B*).

The lateral group of subependymal vei is represented in the frontal horn by t anterior caudate veins (Fig. 4, *A–D*). Pa ticularly in the anteroposterior projectio it may be difficult to distinguish these vei from tributaries of the septal vein. In the la eral view, the largest branch usually aris above the head of the caudate nucleus. Th vein has a typical curved course, co vexity posteriorly, and joins the posteri terminal vein in the floor of the later ventricle along the stria terminalis (Fi 6*B* and 7*A*). A large anterior caudate ve may enter the internal cerebral vein ind pendently of the posterior terminal ve (Fig. 8*A*). Minor variations in this uni are not uncommon (Fig. 5, *A* and *B*; ar 6*A*). Rarely, an anterior caudate vein m join a septal vein to form a separate tru

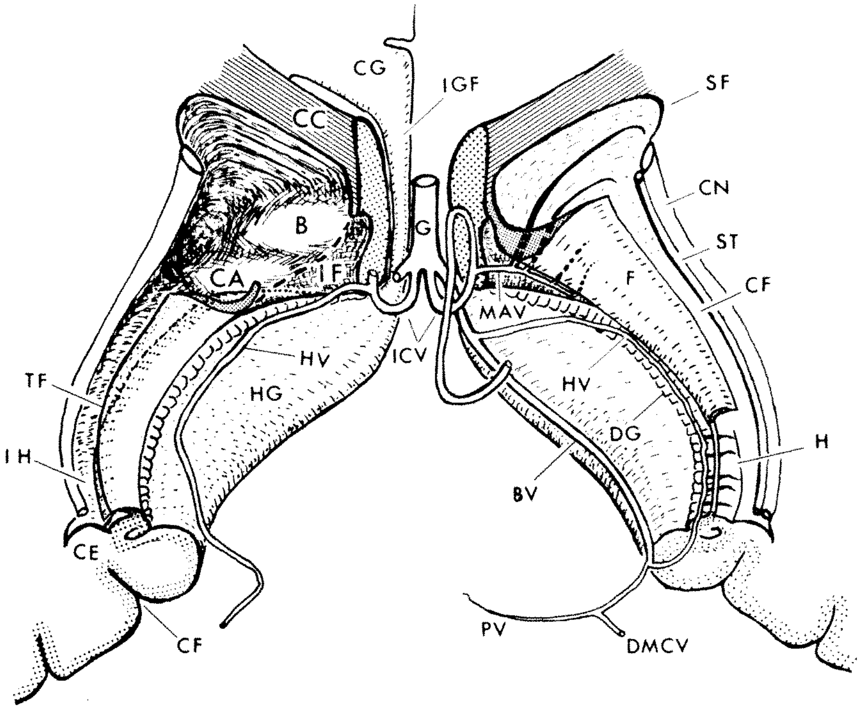

Fig. 10. Diagrammatic representation of the anatomic relationships of the medial atrial veins and veins of the hippocampal formation. The view is from the front after removal of the anterior portion of the lateral ventricle, the thalamus and the brain stem. In a rough way, the structures in this figure may be visualized as fitting behind the structures shown in Figure 1*B*. Labeled structures include the stem of the medial atrial vein (MAV), the longitudinal hippocampal vein (HV), the basal vein (BV), the internal cerebral vein (ICV), the great vein of Galen (G), the deep middle cerebral vein (DMCV), the peduncular vein (PV), the cingular gyrus (CG), the isthmus of the gyrus fornicatus (IGF), the corpus callosum (CC), the bulb of the atrium and posterior horn (B), the calcar avis (CA), the inferior fasciculus (IF) of the forceps major, the tenia fimbria (TF), the cavity of the inferior horn (IH), the collateral eminence (CE), the collateral fissures (CF), the fornix (F), the hippocampal gyrus (HG), the dentate gyrus (DG), the superior occipito-frontal fasciculus (SF), the tail of the caudate nucleus (CN), the stria terminalis (ST), the choroidal fissure (CF), and the hippocampus (H). The central portion of the splenium has been removed to expose the great vein of Galen and the veins joining it. On the reader's right, four veins from the medial wall of the atrium are illustrated appearing extraventricularly along the medial margin of the fornix. These combine to form a short stem (MAV) which runs medially, downward and forward to join the posterior portion of the internal cerebral vein. Numerous small transverse veins over the hippocampus (H) also exit along the medial margin of the fimbria of the fornix to join a longitudinal stem (HV) which runs parallel to the dentate gyrus. This vein is shown joining the basal vein both anteriorly and posteriorly. On the reader's left, a similar but larger longitudinal vein (HV) is shown which may replace the basal vein. Note the broad superior surface of the hippocampal gyrus. The basal vein usually runs in relationship to the medial border of this surface and its continuation into the isthmus gyrus fornicatus.

(Fig. 13, *A* and *B*), which runs for some distance below the internal cerebral vein before entering it.

In the body of the ventricle, the prototype vein of the lateral group is the vessel described by Browning as the "direct lateral vein." This vessel may be quite prominent when the posterior terminal vein is small (Fig. 14; and 15, *A* and *B*). In such instances, the anterior tributary of this vessel may replace the posterior terminal vein. The direct lateral vein receives several tributaries from the lateral wall of the posterior portion of the body of the ventricle and occasionally from the adjacent lateral wall of the atrium. The

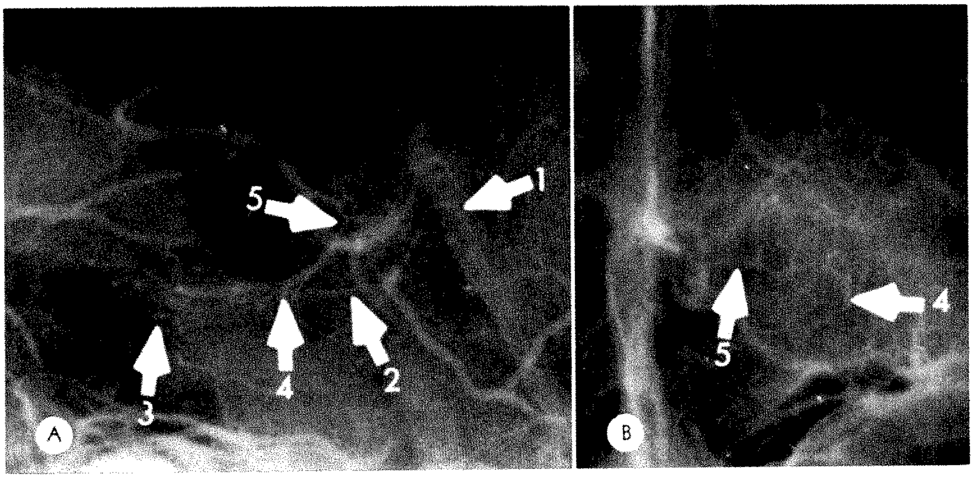

Fig. 11. Posterior horn and hippocampal veins.

(*A*) Lateral projection shows several small medial atrial veins (1) beginning in the posterior horn and extending forward in the wall of the atrium. In addition, there is a small vessel (2) in the posterior portion of the floor of the inferior horn which also begins in the posterior horn but extends directly forward. Several irregular faintly seen vessels in the floor of the temporal horn extend for some distance in front of and in line (3 to 4) with this latter vessel. A common stem is formed (4) which then extends upward and backward (partially obscured by the basal vein) to join the medial atrial vein (5). This stem and the junction with the medial atrial vein lie outside the ventricle. The small veins in the floor of the temporal horn (veins of the hippocampus) are part of the medial group of veins since their mode of exit deep to the fornix is similar to the medial atrial veins and these vessels may communicate with each other.

(*B*) Anteroposterior projection shows a small channel (4 to 5) extending backward and medially in an arcuate configuration. This longitudinal hippocampal vein runs outside the ventricle parallel to the dentate gyrus. Multiple short vessels on the ventricular aspect of the hippocampus join this stem at a right angle, suggesting a rake appearance.

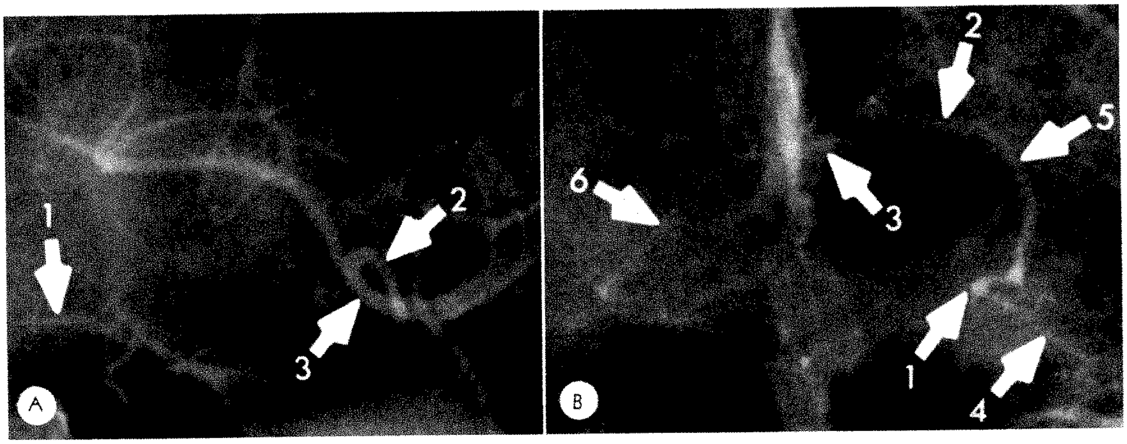

Fig. 12. Longitudinal hippocampal vein replacing the basal vein.

(*A*) Lateral projection shows a large vein beginning in the usual location of the basal vein (1) above the sella turcica and extending backward in rather typical fashion. The terminal portion of the vessel, however, is unusual for the normal basal vein since it ascends to a point (2) above the level of the internal cerebral vein and then loops forward and downward to join the posterior end (3) of the internal cerebral vein.

(*B*) In the anteroposterior projection, there is less resemblance of this vein to the normal basal vein. While it appears to begin (1) by draining the transverse trunk of the deep middle cerebral vein (4) and runs upward and backward, it is located unusually far laterally (5). As a result, this vein has a long transverse course posteriorly (2) and it runs medially to join the internal cerebral vein (3). Since the basal vein of the opposite side is faintly visualized (6), the difference in the courses of these two vessels is clearly demonstrated.

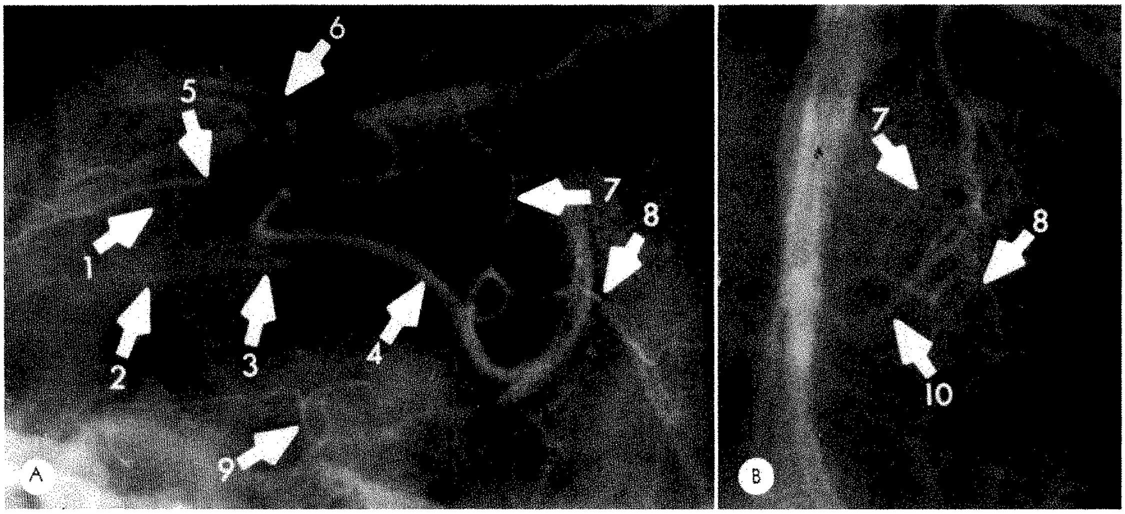

FIG. 13. Anomalous anterior caudate and septal veins.

(*A*) In the lateral projection, an anterior caudate vein (1) and a septal vein (2) join in the region of the foramen of Monro to form a common stem (3) which runs backward below the internal cerebral vein to join the posterior portion of this vein (4). The main septal vein (5) joins the internal cerebral vein a short distance behind its anterior end. Additional anterior caudate veins (6) join the striothalamic vein in typical fashion. A characteristic medial atrial vein is present. It is formed by an anterior branch (7) and a large branch from the posterior horn (8) which unite to form a transverse trunk extending into the great vein of Galen. A short stem (9) draining small tributaries from the roof of the tip of the temporal horn can be seen entering the anterior portion of the basal vein.

(*B*) In the anteroposterior projection, the typical configuration of the striothalamic vein (10) is well shown. The two tributaries (7, 8) of the medial atrial vein unite to form a short trunk which runs medially to join the vein of Galen. The stem formed by the anomalous anterior caudate and septal veins is obscured in this view by the internal cerebral vein and longitudinal sinus.

transverse caudate veins running downward from the superior lateral angle of the body of the ventricle may join the direct lateral vein and occasionally form its major tributaries. The stem or trunk of the direct lateral vein runs directly medially in the frontal plane underneath the stria terminalis, lamina affixa and tenia choroidea to enter the velum interpositum and the posterior portion of the internal cerebral vein. Sometimes this stem shows an acute anterior loop (Fig. 15*A* and 16*A*) and appears to be simply a striothalamic trunk

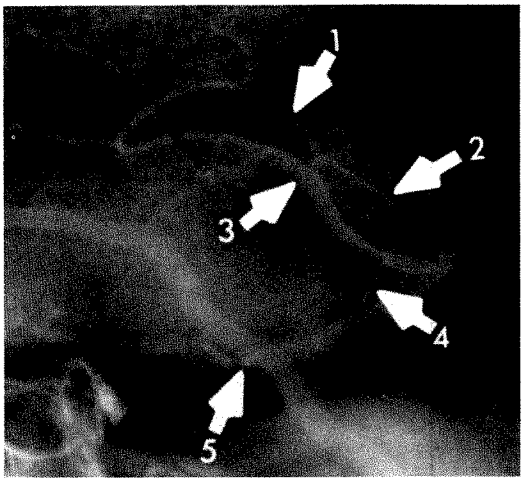

FIG. 14. Lateral projection. Direct lateral vein. The posterior terminal vein (1) runs backward to join several tributaries (2) arising in the lateral wall of the posterior portion of the body of the ventricle. A short stem is formed which runs transversely into the internal cerebral vein (3). A small inferior ventricular vein (4) is also present. The lower portion of this vessel is obscured by the basal vein but its most anterior or transverse segment is evident as a dot (5) superimposed on both vessels.

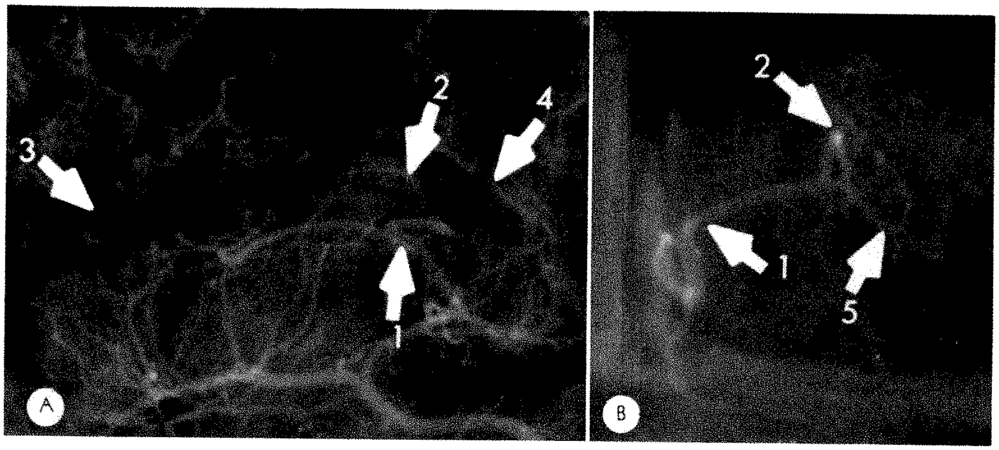

Fig. 15. Direct lateral vein.

(*A*) Lateral projection. A rather large direct lateral vein is seen to enter the posterior portion of the internal cerebral vein (1). A short anterior tributary (2) runs backward to join the main stem. Several unusually prominent longitudinal caudate veins extend from the anterior horn (3) to this tributary (2). These vessels must be distinguished from cerebral veins on the superior aspect of the corpus callosum. The posterior cerebral or splenial vein (4) is quite large in this case and is clearly at a higher level than the longitudinal caudate veins. Moreover, the splenial vein enters the posterior portion of the great vein of Galen near the straight sinus.

(*B*) Anteroposterior projection demonstrates that the direct lateral vein has a surprisingly long transverse course before it enters the internal cerebral vein (1). The anterior tributary (2) is arched superiorly. A more lateral and posterior tributary (5) drains a group of small vessels outlining the lateral wall of the atrium.

which does not extend as far forward as the usual striothalamic vein but enters the internal cerebral vein behind the foramen of Monro. Since this vessel must run underneath the broad free portion of the body of the fornix (Fig. 2*A*), the main stem of this vessel cannot be located more posteriorly than the fornix itself. In the lateral projection, one can imagine the course of the fornix as a curved line crossing the splenial indentation on the great vein of Galen (Fig. 1*A*), a short distance in front of the lowest point of this indentation. In the anteroposterior projection, the direct lateral vein shows a long transverse course (Fig. 15*B*) as it runs underneath the fornix and above the thalamus (Fig. 2*A*). As it extends medially, it runs only slightly downward. This is in contrast to the appearance of the normal striothalamic vein which extends forward and downward to the foramen of Monro and therefore shows a U-shaped configuration, convexity inferiorly, and in the anteroposterior projection (Fig. 7*B*, 8*B*). Small branches arising in the lateral wall of the atrium and joining the direct lateral vein can sometimes be identified and serve to outline the most lateral aspect of the atrium (Fig. 15*B*). In the majority of instances, the direct lateral vein is not a large vessel and its drainage area is taken over by the posterior terminal vein, the lateral atrial or inferior ventricular vein. In the lateral projection, it may be difficult to distinguish a direct lateral vein from the medial atrial vein. In such instances, an anterior tributary corresponding to the course of the stria terminalis, *i.e.*, in line with the posterior terminal vein, indicates that the vessel belongs to the lateral group while a typical posterior horn tributary places the vessel in the medial group.

In the lateral wall of the atrium, there may be a sizable vessel (Fig. 16, *A* and *B*; and 17) which runs downward and forward for a relatively short distance and turns medially to exit through the posterior por-

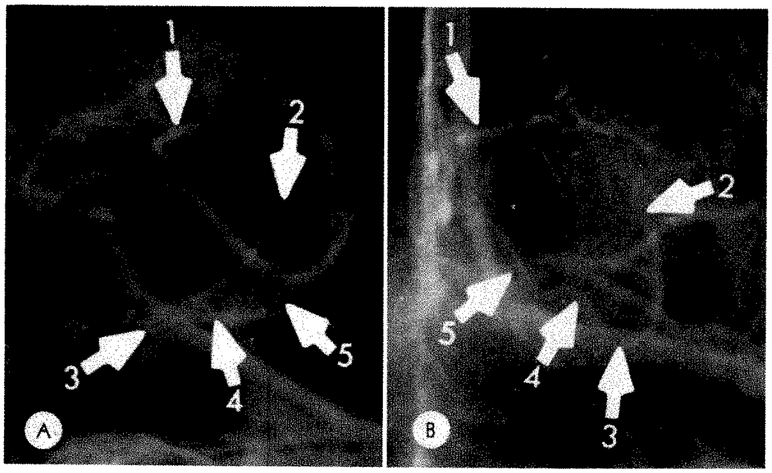

FIG. 16. Lateral atrial vein.

(*A*) Lateral projection shows a direct lateral vein (1) joining the posterior portion of the internal cerebral vein. In addition, there is a prominent vein which begins high on the lateral wall of the atrium (2) by draining several twigs arising posteriorly. This vein runs downward and forward with a slight convexity posteriorly and then crosses medially in the roof of the temporal horn (3) to leave the ventricle through the posterior portion of the choroidal fissure (between 3 and 4) and join the basal vein (5). The basal vein is partially overlapped by a superficial temporal vein.

(*B*) Anteroposterior projection shows the horizontal course of the direct lateral vein (1). The lateral atrial vein (2) begins further laterally and posteriorly and extends forward and downward with a minimal convexity laterally. It then curves medially (3) to pass through the posterior portion of the choroidal fissure (between 3 and 4) and enters the basal vein (5).

tion of the choroidal fissure. This vein may then enter the basal vein or continue posteriorly outside the ventricle parallel to the stria terminalis to enter the direct lateral vein. This vessel was clearly described by Browning[1] under the name "ramus basilaris adjunctus." Since this designation is not only awkward but appears not particularly suitable, we prefer to call this vein "the lateral atrial vein." The lateral atrial vein may be seen in the lateral projection to be formed by small twigs from the upper (Fig. 16, *A* and *B*; and 17) or lower aspect (Fig. 6*A*) of the lateral wall of the atrium and to run obliquely downward and forward toward

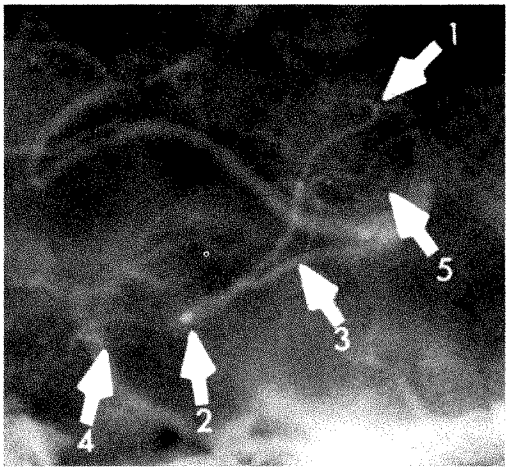

FIG. 17. Another example of a lateral atrial vein. Lateral projection shows a prominent vein beginning high on the lateral wall of the atrium (1) by the junction of small twigs arising both anteriorly and posteriorly. The vessel runs downward and forward in the temporal horn and then turns medially (dense dot, 2) to join the basal vein (3). Several small vessels (4) arising in the roof of the tip of the temporal horn run posteriorly to join this vein. In this case, the lateral atrial vein extends unusually far forward in the roof of the temporal horn and takes over the drainage area of the inferior ventricular vein. Several small medial atrial veins (5) can also be seen.

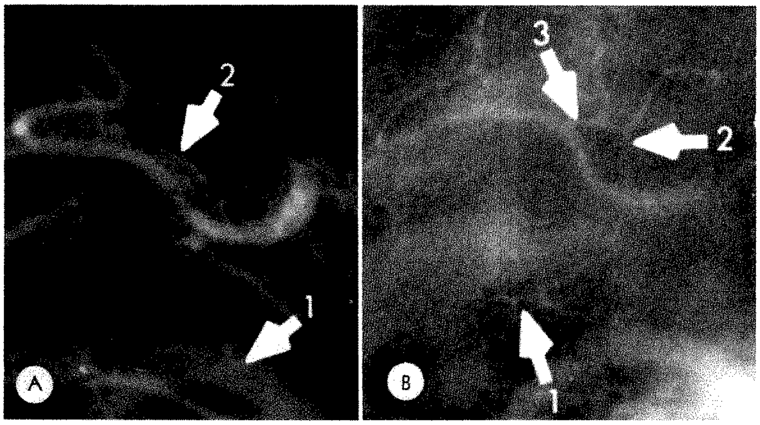

Fig. 18. Superior drainage of atrium or temporal horn.

(*A*) Lateral projection. There is a long lateral atrial vein which begins near the floor of the atrium (1) and runs upward and forward to join (2) the posterior terminal vein.

(*B*) Another patient. Lateral projection. A small inferior ventricular vein begins (1) in the anterior portion of the roof of the temporal horn and runs upward and backward to join (2) a tributary of a direct lateral vein (3).

the inferior horn. This vessel may have a rather straight course or show a slight posterior convexity. In the anteroposterior projection, this vein begins posteriorly about 2.5 cm. from the mid-line and runs downward with a slight lateral convexity. After a relatively short downward course, the vessel turns medially with a rather marked convexity inferiorly and then loops backward to join the basal or adjacent vein. The course of this vessel in both the lateral and anteroposterior projections may resemble the appearance of the inferior ventricular vein to be described below. In its characteristic form, however, the upper posterior portion of the vessel is not adjacent to the caudate nucleus but lies more posteriorly and superiorly. Moreover, the lateral atrial vein passes through the posterior portion of the choroidal fissure rather than through its anterior end in the inferior horn. When the lateral atrial vein is large, the inferior ventricular vein is absent (Fig. 17) or small and vice versa. In some instances, drainage from the lateral wall of the atrium and adjacent roof of the temporal horn is superiorly into a posterior terminal (Fig. 18*A*) or direct lateral vein (Fig. 18*B*).

There is often a surprisingly large vein (Fig. 19, *A* and *B*; and 20, *A* and *B*) in the roof of the temporal horn which is the representative of the lateral group of subependymal veins in this area. This vessel (Fig. 4, *A–D*) begins in the body of the ventricle along the superior margin of the body of the caudate nucleus and runs in a markedly curved course downward and backward and then forward into the inferior horn. The course of this vein appears to parallel rather exactly the body and the tail of the caudate nucleus. This vein may therefore be located in three different portions of the ventricular system, namely, the posterior portion of the body, the anterior wall of the atrium, and the roof of the temporal horn. When large, this vessel serves as a longitudinal collecting channel similar or complementary to the posterior terminal vein. This vessel was described by Browning,[1] who called it the "inferior ventricular vein." An alternative designation for this vein, when of large size, is the "atriotemporal vein" since both the lateral wall of the atrium and the roof of the temporal horn may be drained by it. As pointed out by Browning, the inferior ventricular vein ordinarily runs in the lateral portion of the roof of the temporal horn, that is, lateral to the caudate nucleus

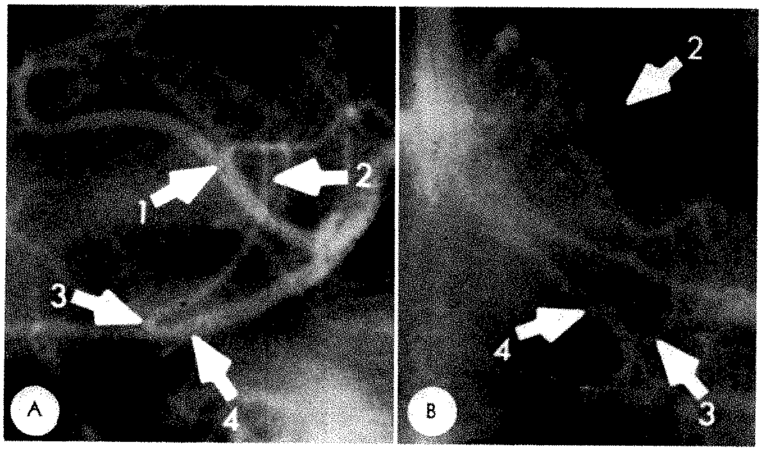

Fig. 19. A large inferior ventricular vein.

(*A*) Lateral projection. A typical direct lateral vein is present joining the posterior portion of the internal cerebral vein (1). The largest vessel in this area, however, begins high in the anterior wall of the atrium (2) and shows a characteristic arcuate course as it runs downward and forward in the roof of the temporal horn. At the anterior end of the choroidal fissure, it turns medially (3) to enter the basal vein (4).

(*B*) Anteroposterior projection. The inferior ventricular vein (2) originates superiorly in the anterior wall of the atrium. The vessel runs downward and forward with a moderate convexity laterally to the anterior portion of the temporal horn and then curves medially (3) to exit through the choroidal fissure and join the basal vein (4). Incidentally, a short distance lateral and parallel to the ventricular portion of this vein, a faint vessel is seen which is the inferior choroidal vein.

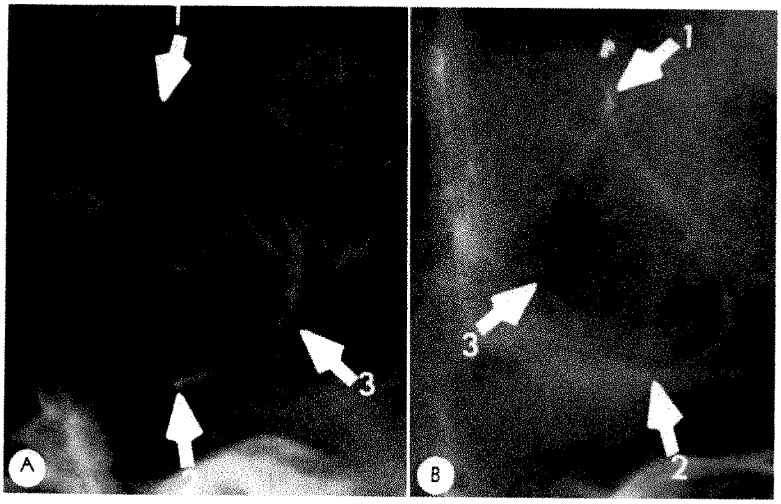

Fig. 20. Unusually long inferior ventricular vein.

(*A*) Lateral projection shows the inferior ventricular vein beginning far forward (1) in the body of the lateral ventricle and forming almost half a circle, convex posteriorly, as it extends downward and backward and then downward and forward to the anterior end of the choroidal fissure (2). This vein runs in the roof of the temporal horn lateral to the caudate nucleus. The basal vein is faintly opacified (3).

(*B*) In the anteroposterior projection, the unusually long inferior ventricular vein indicates the location of the body and tail of the caudate nucleus since it is located immediately lateral to this structure. In the body of the ventricle (1), it is at a slightly higher level than the stria terminalis. The vein runs downward and laterally and then turns medially in a broad arcuate course to leave (2) the inferior horn and join the basal vein (3).

and therefore cannot be considered as a direct continuation of the posterior terminal vein. In unusual instances, however, this vessel may be located more medially in the roof of the temporal horn, adjacent to the stria terminalis. In the lateral projection, the inferior ventricular vein shows a very characteristic arcuate appearance, convexity posteriorly, with an abrupt termination in the anterior portion of the basal vein at a point about 2 cm. behind the posterior clinoids. The inferior ventricular vein crosses the splenial indentation on the vein of Galen in front of its lowest point. This arcuate course is similar to that of the fornix since the fornix and the tail of the caudate nucleus run parallel to each other (Fig. 10). In the lateral projection, it is not possible to tell the exact relationship of this vein to the tail of the caudate nucleus in the inferior horn. However, it is usually evident that the portion of this vessel in the body of the ventricle is located at a higher level than the stria terminalis (Fig. 20, *A* and *B*). In the anteroposterior projection, the inferior ventricular vein has a very typical appearance, beginning posteriorly about 2 cm. from the mid-line and extending downward and forward with a moderately marked lateral convexity. In the tip of the temporal horn, the vessel turns medially in a fairly abrupt but smooth curve, convexity anteriorly, to reach the anterior end of the choroidal fissure immediately behind the uncus. In this transverse portion of its course, this vein receives several small twigs from the tip of the temporal horn. At the point of exit in the choroidal fissure, it is joined by the inferior choroidal vein and the common stem enters the basal vein. The relationships of the inferior ventricular vein and the choroidal vein of the temporal horn are therefore similar to that of the striothalamic stem and the superior choroidal vein at the foramen of Monro. In an occasional instance, a small inferior ventricular vein may not drain downward and forward but rather upward and backward into the direct lateral (Fig. 18*B*) or the posterior terminal vein. Incidentally, the course of the inferior ventricular vein in the lateral projection corresponds rather closely to the appearance of the wing of the cisterna ambiens as seen during pneumoencephalography. However, the lateral margin of the wing of the cisterna ambiens corresponds to the choroidal fissure while the inferior ventricular vein is located more laterally within the ventricle.

Veins in the roof of the tip of the temporal horn (Fig. 13*A* and 17) may join to form a short trunk which leaves the ventricle through the anterior end of the choroidal fissure independently of the inferior ventricular vein. Small tributaries may run forward in the temporal horn along the stria terminalis to join this trunk. These tip vessels may be relatively prominent and evident on angiography particularly when the inferior ventricular vein is small.

On angiography, the subependymal veins must be differentiated from superficial veins which frequently overlap them. This distinction is usually not difficult since superficial veins are more tortuous, extend beyond the anticipated area of the ventricular system and drain into dural sinuses[10] or the anterior end of the basal vein.[11] In general, subependymal veins are not tortuous, change caliber abruptly at points of union with adjacent vessels and they drain into the internal cerebral vein, vein of Galen, or into the basal vein behind the anterior perforated space. Despite the rather characteristic features of the subependymal veins described above, it is not always possible to be certain in every case of the location of a particular vessel. This is often due to the fact that the venous phases in the anteroposterior projection are difficult to interpret because of technical problems and overlapping vessels. In the lateral projection, identification is facilitated by the observation that veins which cross each other cannot lie in the same plane. By systematically following the course of the individual tributaries and observing this crossing sign, it is usually possible to distinguish between the medial and lateral groups of vessels. Stereoscopic or base views should presumably be of considerable assistance in making this differentiation but are not generally available.

For purposes of angiography, the system of subependymal veins has been considered as a unit more or less by itself. Obviously, however, these veins drain the substance of the brain rather than the subependymal tissues. They share drainage of the cerebral hemispheres with the superficial veins. In a rough way, the vein of the septum pellucidum drains the deep part of the frontal pole, the lateral system of veins drains the lateral portion of the hemisphere, while the medial atrial vein drains the occipital pole. In general, one can anticipate filling of all components of the subependymal venous drainage system of the lateral ventricle if there has been satisfactory opacification of the anterior, middle and posterior cerebral arteries. The medial atrial veins, however, may not be evident on carotid angiograms if the posterior cerebral artery is not filled. There is often considerable asymmetry in the individual components on the two sides. The two veins of the septum pellucidum, however, are usually similar in configuration. Incidentally, there appear to be no anastomoses between the ependymal veins of the lateral ventricles of the two sides. Except for the striate veins, the small veins within the brain substance are rarely evident on angiography. This is of some advantage because the visible veins can then be identified as either superficial or subependymal in location. In this sense, both of these venous systems are made up of surface vessels.

In the description of the subependymal veins given above, the choroidal veins were mentioned only in passing. These vessels are in reality not subependymal in location and serve primarily for cerebrospinal fluid formation rather than drainage of the brain substance. Small channels from the brain substance described anatomically which may enter choroidal veins are rarely evident on angiography.

The classification given above of the subependymal veins was designed for practical diagnostic purposes. On an anatomic and presumably developmental basis, a more pertinent division may be based on the sites of exit of the subependymal veins, that is, the locations at which they cease to be subependymal and enter the subarachnoid space. These veins may be said to enter the subarachnoid space in relationship to the two aspects or margins of the fornix and its extensions. The vein of the septum pellucidum and the most anterior of the posterior septal veins run in relationship to the lateral margin of the column of the fornix before joining the internal cerebral vein in the velum interpositum. The entire lateral group of veins including the striothalamic vein enters the velum interpositum by running deep to the stria terminalis, the lamina affixa, and tenia choroidea through the choroidal fissure. In contrast, the small deep veins in the septum pellucidum, the medial atrial veins and the floor veins of the temporal horn pierce the medial attached portions of the fornix in order to enter the subarachnoid space. This last group of vessels does not run in relationship to the tenia fimbria or the choroidal fissure. This mode of exit of the medial group of veins has apparently not been previously emphasized. The embryologic significance of these distinctions is not clear.

From the diagnostic point of view, recognition of abnormalities of the subependymal veins is based primarily on familiarity with the normal configurations of these vessels as components of an interdependent venous drainage system. The individual members may vary in size and their drainage areas may be absorbed by adjacent vessels. Efforts to be more specific in regard to the location of these veins by measurement are of limited use because of considerable normal variation. Several rough guide numbers, however, may be noted. The distance between the mid-line and the most lateral point of the inferior ventricular vein in the anteroposterior projection (target-film distance 40 inches) varies from 2.5 to 3.5 cm. The distance in the lateral projection between the point at which the inferior ventricular vein crosses the vein of Galen and the center of the sella turcica is 4.5 to 5.5 cm. The distance in the lateral projection between the lowest point of the inferior ventricular vein in the temporal horn and the posterior terminal vein along the stria terminalis in the body of the ventricle is 2.5 to 3.5 cm.

SUMMARY

1. In the lateral ventricles, numerous subependymal veins are described anatomically and may often be recognized on cerebral angiography.

2. These vessels may be divided into medial and lateral groups. In each group, rather characteristic veins are present in the different portions of the ventricle—anterior horn, body of the ventricle, atrium and posterior horn, and inferior horn.

3. The anatomic and roentgen appearance of the subependymal veins and their interrelationships are described and illustrated.

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Vol. 91, No. 2

THE MYELOGRAPHIC DEMONSTRATION OF THE ANTERIOR SPINAL AND RADICULAR ARTERIES*

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THE spinal cord is visible on cervical and thoracic myelograms as a central radiolucent streak produced by displacement of pantopaque into the deep lateral aspects of the canal and the relatively thin anterior and posterior spaces above and beneath the cord. When the canal is filled completely, the larger quantities of pantopaque may render this shadow less conspicuous than seen with partial filling. When enough pantopaque enters the upper cervical spinal canal and the cisterna magna, the vertebral and basilar arteries can be identified similarly as relatively slender radiolucent linear structures corresponding to their anatomic positions. Little comment has been made about the myelographic appearance of the anterior spinal and radicular arteries, structures which often are seen on technically adequate roentgenograms.

In the upper cervical spinal canal, the anterior spinal artery is formed by the union of two small vessels originating from the medial aspects of the vertebral arteries above the level of the posterior inferior cerebellar arteries. The originating vessels may be asymmetric, corresponding in size relative to the caliber of the vertebral arteries from which they arise. These two rootlets unite in the midline at the level of the medulla oblongata and then pass caudally as the anterior spinal artery in the anterior spinal sulcus. The myelographic demonstration of the V-shaped roots of the anterior spinal artery has not been identified on myelograms insofar as I know. They were visible in 3 of the 50 cervical myelograms utilized for the present study (Fig. 1, *A* and *B*).

A variation of this structure was noted during the course of reviewing 20 specimens of the spinal cord for the purpose of correlating the anatomic and myelographic configuration of the anterior spinal and radicular arteries. In 3 instances the caudad union of the roots of the anterior spinal artery did not conform with the classical V-shaped configuration. In these the rootlets emerging from the medial aspects of the respective vertebral arteries were single, but their fusion into the midline anterior spinal artery (Fig. 1*C*) in the anterior spinal sulcus could not be clearly identified. The rootlets apparently broke up into smaller filaments which traversed the pia and arachnoid on either side of the midline of the medulla oblongata and then dipped into the spinal cord so that the usual clean cut V-shaped origin of the main midline trunk could not be traced.

The anterior spinal artery (Fig. 2, *A* and *B*) courses down the midline in the anterior spinal sulcus enveloped in the pial fold of the linea splendens and terminates along the filum terminale. The respective inferior halves of the spinal cord derive their arterial supply from the sulcal arteries which pass dorsally into the cleft from the anterior spinal trunk, a pattern followed for the entire length of the cord. Below the upper cervical level the anterior spinal artery is derived from and receives blood from the ascending branch of the anterior radicular arteries when these vessels reach the midline. The cervical radicular arteries originate from the vertebral and anterior cervical arteries, the latter being branches of the ascending cervical branches of the inferior thyroid artery. The radicular branches to the thoracic portion of the anterior spinal artery are derived from ascending and descending branches from the intercostal arteries (Fig. 3, *A* and *B*). The lumbar

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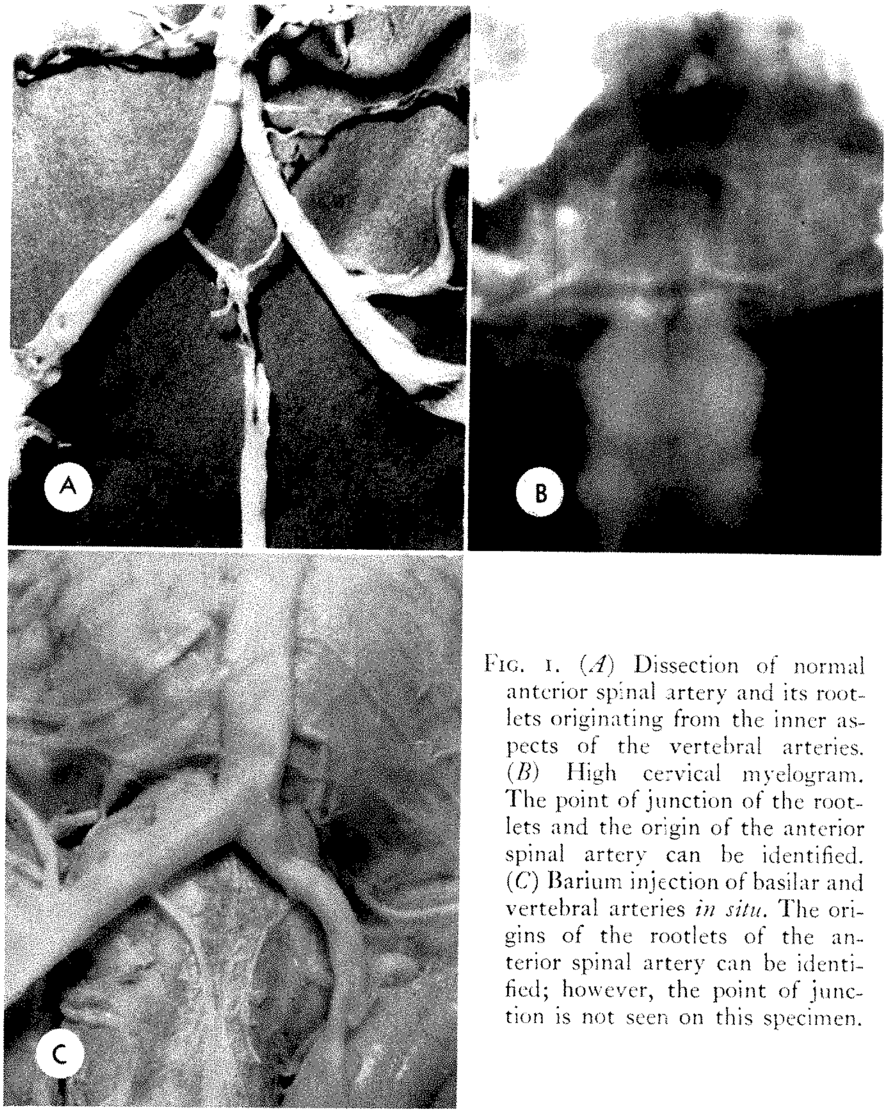

Fig. 1. (*A*) Dissection of normal anterior spinal artery and its rootlets originating from the inner aspects of the vertebral arteries. (*B*) High cervical myelogram. The point of junction of the rootlets and the origin of the anterior spinal artery can be identified. (*C*) Barium injection of basilar and vertebral arteries *in situ*. The origins of the rootlets of the anterior spinal artery can be identified; however, the point of junction is not seen on this specimen.

radicular arteries arise from the iliolumbar and lateral sacral arteries in the pelvis.

There are usually from 6 to 8 large anterior radicular arteries. The largest is situated in the lumbar or lower thoracic region as a single vessel, the arteria radicularis magna. Next in size are the cervical and lower thoracic radicular arteries. In the cervical region the radicular arteries appear at the third, fourth, fifth or sixth segments, and are quite variable in size and distribution. As a rule, 1 is present in the upper cervical region and 2 or 3 in the lower cervical area. In the thoracic spinal canal 1 or 2 are usually present in the upper and lower thoracic regions respectively.

The anterior spinal artery thus is formed by anastomosing vessels originating from the ascending and descending branches of the various radicular arteries. The areas of the cord best supplied with blood are those in proximity to the radicular arteries at their origins. The caudad and cephalad ends of the respective vessels usually provide less blood to their spinal segments. In general, this occurs mainly at about the fourth or fifth thoracic vertebral level, and to a lesser degree at the thoracolumbar junction.

The truncus venosus anterior is derived from radicular veins which do not correspond in location to the arteries but are of

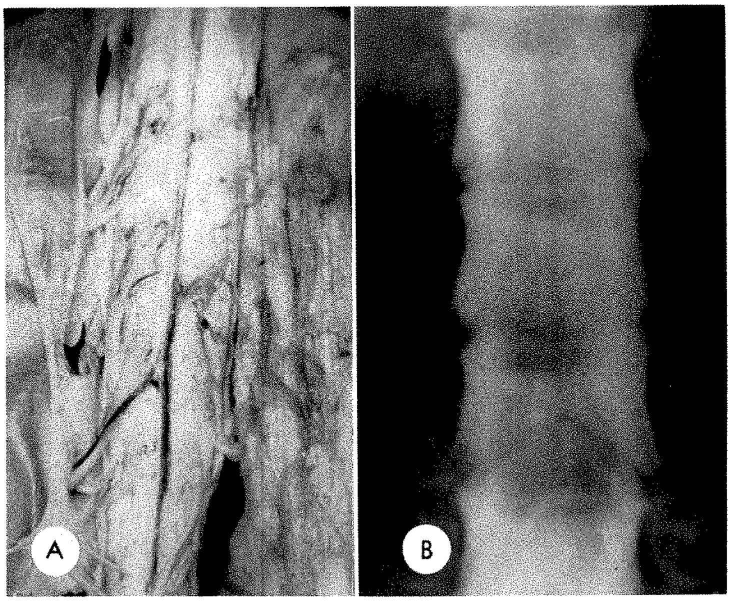

Fig. 2. (*A*) Dissection of the anterior spinal artery in the midcervical and lower cervical region. The midline position of the artery and one major right radicular artery can be identified. Note the rounded junction of the radicular artery with the main trunk. (*B*) Cervical myelogram. The anterior spinal artery is visible as a midline radiolucent streak. A radicular branch is present on the left side.

approximately the same size. The truncus venosus anterior lies slightly to the side of the anterior spinal artery and just dorsal to it, and also is invested by the linea splendens. No doubt it contributes to the myelographic appearance.

On frontal and oblique myelograms the anterior spinal artery is best seen in the upper two thirds of the cervical spinal canal, and is identified as a relatively straight radiolucent midline streak often interrupted at the level of the intervertebral disks. This is attributed to the relative depth of pantopaque overlying the dorsal aspects of the vertebral bodies as compared to the more shallow or even absent layer above the bulging intervertebral fibrocartilages. Where there is sufficient pantopaque to be displaced by the slightly anteriorly protruding anterior spinal artery, its linear shadow becomes visible. If the relative depth of pantopaque is thin, as it is in relationship to the disks, no shadow is seen. This change is more pronounced when spondylotic ridges project into the ventral aspect of the cervical spinal canal. On oblique myelograms the shadow of the anterior spinal artery shifts laterally. It is considerably more difficult to identify the vessel in this projection because of conflicting shadows produced by

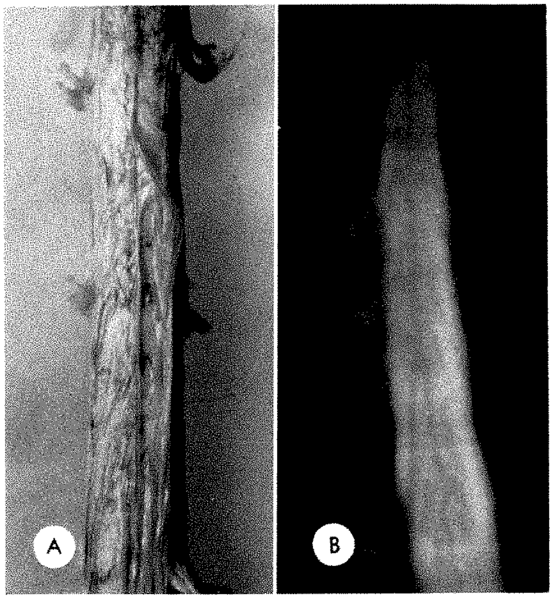

Fig. 3. (*A*) Dissection of the anterior spinal artery in the midthoracic region. (*B*) Thoracic myelogram showing the anterior spinal artery and several radicular branches. Note the irregularity in the course of the anterior spinal artery in its lower aspect on this roentgenogram.

the dentate ligaments and the rootlets of the spinal nerves as well as by the changes in the position of the pantopaque.

The radicular branches to the anterior spinal artery are seen anatomically in close relationship to the superior aspects of the anterior nerve roots. On comparing the myelographic with the anatomic appearance, it was observed that not infrequently there were small branches extending along the intrathecal aspects of the nerve roots which were thin and could not be identified roentgenologically. The junctions of the anterior spinal and radicular arteries could be utilized to identify these structures by virtue of their midline positions.

The posterior spinal arteries exist as irregular paired structures on either side of the cord. These also accept radicular vessels, but neither the main plexuses nor their feeding branches could be identified on myelograms.

In order to estimate the clinical significance of visualization of the anterior and radicular spinal arteries, 50 consecutive thoracocervical myelograms were reviewed. Of these 28 were considered to be within average limits even though 11 showed some evidence of cervical spondylotic ridging. In 9 examinations the thoracic portion of the anterior spinal artery could be seen, and in none of these was any additional information obtained. There were 7 patients with tumors in the spinal canal, and in but 1 was there enough contralateral displacement of the anterior spinal artery to warrant any comment. Of the 15 patients with significant lower cervical spondylotic spurring or diskal herniation, the upper aspect of the anterior spinal artery was more apparent, and in all the anterior spinal artery overlying the diskal spurs or ridges in the midline was not visible. In 5 instances with large midline ridges and partial obstruction to the passage of pantopaque, there appeared to be a slight but perceptible increase in the caliber of the anterior spinal artery above the affected areas. In general, it was felt that no specific diagnostic significance could be attributed to the visualization of the anterior spinal and radicular arteries.

SUMMARY

The anatomic and myelographic appearance of the anterior spinal and radicular arteries is described. No specific diagnostic information could be elicited from the visualization of these vessels.

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A STUDY OF MENINGIOMAS WITH CORRELATION OF HYPEROSTOSIS AND TUMOR VASCULARITY*

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THE number of publications on meningiomas is so extensive that, as Bailey[1] stated, "another paper taking up this question requires considerable temerity." Many aspects of meningeal tumors have been described: their appearance in the plain skull roentgenogram, in the pneumoencephalogram and in the arteriogram. The histology of these tumors is well known although the diagnosis may not always be conclusive if the classic histologic tumor pattern is absent. Surgical exploration of meningeal tumors has attained excellent results, but profuse bleeding from a highly vascular tumor remains a considerable hazard. It is important for the surgeon to know in which type of meningioma operative bleeding may be expected. An attempt has been made to correlate the degree of vascularity of a meningioma with bone changes, in particular, hyperostosis produced by such a tumor, in order to find a possible association between vascularity and hyperostosis. This aspect has received, in the literature, no consideration up to this date.

SURVEY OF THE LITERATURE

The earliest description of hyperostosis in the restricted sense dates back to 1903 by Brissaud and Lereboullet.[2] The condition was termed hemicraniosis because the bone thickening involved half of the skull and face. The etiology of this condition was then unknown. Spiller[13] in 1907 first pointed out that pronounced local thickening of the skull was likely to be associated with a tumor of the meninges. In 1929 he[14] expressed the view that hyperostosis produced by trauma, syphilis or any other factor might cause irritation leading to the formation of an underlying fibroblastoma. Cushing,[3] who found bone thickening in 25 per cent of his meningioma series, believed that hyperostosis was produced by "insinuation" of the tumor cells into the vascular spaces of the bone. The "crowding" of tumor cells in the vascular space, he thought, might act as an irritant producing osteoblastic proliferation. Phemister[11] considered the possibility that hyperostosis developed as a result of tumor permeation of the skull table by a mesoblastic tumor originating outside bone. Kolodny,[7] however, affirmed that the bone proliferation preceded the actual infiltration of bone by tumor cells and was most likely the result of an early and particularly slow progressive dilatation of blood vessels in the skull adjacent to the meningioma, while the subsequent infiltration might lead to bone destruction.

Enostosis is the first reaction of bone to an underlying meningioma. Bone thickening ensues and hyperostosis with radiating spicule formation represents the final condition of the osteoblastic activity of the bone.[3] Diffuse thickening of the skull base is mainly associated with olfactory groove and sphenoidal wing meningiomas.[12] The great thickening is in contrast with the extremely small amount of tumor tissue present in the bone.[17]

With the advent of angiography, the vascular pattern of meningiomas was more thoroughly investigated. Out of the large volume of literature, only a few pertinent and explanatory references to the vascular pattern of meningiomas need be mentioned.

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Lima[8] recognized that every meningioma is supplied by the external and internal carotid arteries. He stated that the afferent vessels penetrated the periphery of the tumor and branch at the center into an arterial network emptying into a rich capillary network, thence to a vein in the periphery of the tumor. He further maintained that a more abundant arterial circulation occurred at the center than on the periphery of the tumor. Wickbom[15,16] classified the meningiomas into 4 groups on the basis of the vascular appearance observed in the roentgenogram: (1) homogeneous accumulation of the contrast medium which might be sharply defined or show an abundance of small vessels with uniform appearance; (2) newly formed vessels, narrow and serpentine, with a regular lumen branching in a broom-like or radial formation; (3) arrangement of the vessels around the tumor with a conspicuously large artery encircling the growth; and (4) a circular arrangement around the tumor with no definite tumor vessels present. Lindgren[9] pointed out that the dual supply of the meningioma could be demonstrated by separate puncture of the internal and external carotid arteries. The internal carotid may supply the periphery of the tumor while the central portion may be supplied by the external carotid artery. Wickbom[15] noted in a few cases in his series that with internal carotid injection a sector of a sphere was outlined with contrast medium. Lorenz[17] pointed out that the vessels surround the tumor "krallenformig" and a large artery is present in the immediate vicinity of the tumor.

The present study was undertaken to examine the various degrees of meningioma vascularity and correlate them with the different types of hyperostosis associated with meningiomas.

MATERIAL

A series of 141 cases diagnosed roentgenologically as meningiomas at the National Hospital, Queen Square, was examined. After selection, only 115 cases from the original 141 could be used for this investigation. Twenty six cases were not included for the various reasons outlined in Table I. All 115 cases had sufficient skull roentgenograms and carotid angiographic studies to be included in this series. Every case was operated upon and had therefore histologic verification. The cases accumulated over a period of 12 years, from 1948 to 1960.

Table I

CASES EXCLUDED FROM MENINGIOMA STUDY

Roentgenograms missing	6
Roentgenograms unsatisfactory	2
Roentgenograms incomplete	2
Roentgenograms in outside Hospitals	3
Negative exploration	1
Not operated upon	1
Gliomas	8
Chromophobe adenoma	1
Myxomatous mesodermal tumor	1
Malignant sarcomatous meningioma	1
Total	26

It should be noted that in only 10 cases was an incorrect diagnosis made (8 gliomas, 1 chromophobe adenoma and 1 negative exploration), comprising a 7 per cent margin of error. One case of myxomatous mesodermal tumor showed components of a meningioma histologically. A correct preoperative diagnosis was not feasible because of the extreme rarity of the tumor. One malignant sarcomatous meningioma, the only such case in this series, was likewise not included. Investigation in 14 cases remained incomplete.

Out of the 115 patients, 52 were males and 63 were females. The youngest was a 12 year old female and the eldest a male 75 years of age. The average age in the females was 48.7 years, while the average age in the males was 48.8 years. The meningiomas occurred in all the classic locations. The distribution and the tumor incidence in the various locations is shown in Table II.

The highest incidence (36.0 per cent) of meningiomas was in the frontoparasagittal region followed by the parietoparasagittal region (29.0 per cent); the lowest incidence (less than 1 per cent) occurred in the base of the middle fossa, middle third of the lesser sphenoid wing and the greater wing of the sphenoid bone and orbit. The remainder of the tumors was distributed among other locations with 2.6 per cent in the subfrontal, olfactory groove, inner third of sphenoid and occipital parasagittal region; 1.7 per cent occurred in the anterior clinoid region, 8.7 per cent in the tuberculum sellae and 9.0 per cent in the pterion region.

METHOD

The plain skull roentgenograms were surveyed and the classic changes of increased intracranial pressure were noted if present (Table III). It was found that demineralization of the floor of the sella turcica and/or of the posterior clinoid processes was present in 73 cases (63.5 per cent). Increased digitation in the internal table of the skull was not noted in any case; there was no case with suture diastasis. The pineal gland was calcified in 67 cases (58.3 per cent). Out of the 115 cases, 40 (34.8 per cent) showed a shift of the calcified pineal on the side opposite to that of the tumor. If, however, the 67 cases with a calcified pineal were considered alone, the incidence of shift would be 25.2 per cent higher (approximately 60.0 per cent).

Table II

LOCATION OF TUMORS

		Total	Per Cent	
Subfrontal	rt. 1 lt. 2	3	2.6	
Olfactory groove	3	3	2.6	
Anterior clinoid	2	2	1.7	
Tuberculum sellae	10	10	8.7	
Pterion	rt. 5 lt. 7	12	9.0	
Middle third of sphenoid wing	rt. 0 lt. 1	1	0.8	
Inner third of sphenoid wing	rt. 2 lt. 1	3	2.6	
Greater sphenoid wing and orbit	rt. 1	1	0.8	
Middle fossa (base)	lt. 1	1	0.8	
Parasagittal and falx (frontal)	rt. 16 lt. 26	42	36.0	67.6
Parasagittal and falx (parietal)	rt. 17 lt. 17	34	29.0	
Parasagittal and falx (occipital)	rt. 1 lt. 2	3	2.6	

Table III

CHANGES ON PLAIN SKULL ROENTGENOGRAMS

1. Sella turcica	
Positive	73 (63.5%)
Negative	42 (36.5%)
2. Pineal gland	
Calcification	67 (58.3%)
Shift	40 (60.0%)
3. Hyperostosis	16 (13.9%)
Enostosis	23 (20.0%)
Diffuse thickening	16 (13.9%)
Vascular channels	59 (51.0%)
Bone erosion	14 (12.0%)
Calcification	9 (7.8%)

Changes on plain roentgenograms which might suggest localization of the tumor were looked for (Table III). Bone changes produced by osteoblastic activity were classified as hyperostosis, enostosis and diffuse thickening of the skull in the diploic space. The accuracy of the survey was somewhat hampered as in none of the examinations was there a tangential view of the affected area of the skull, which is essential for complete examination. A number of small enostoses was not demonstrable because of lack of tangential views. There were 16 cases of hyperostosis (13.9 per cent), but in none of these was the so-called typical spicule formation demonstrated roentgenographically. A study of earlier

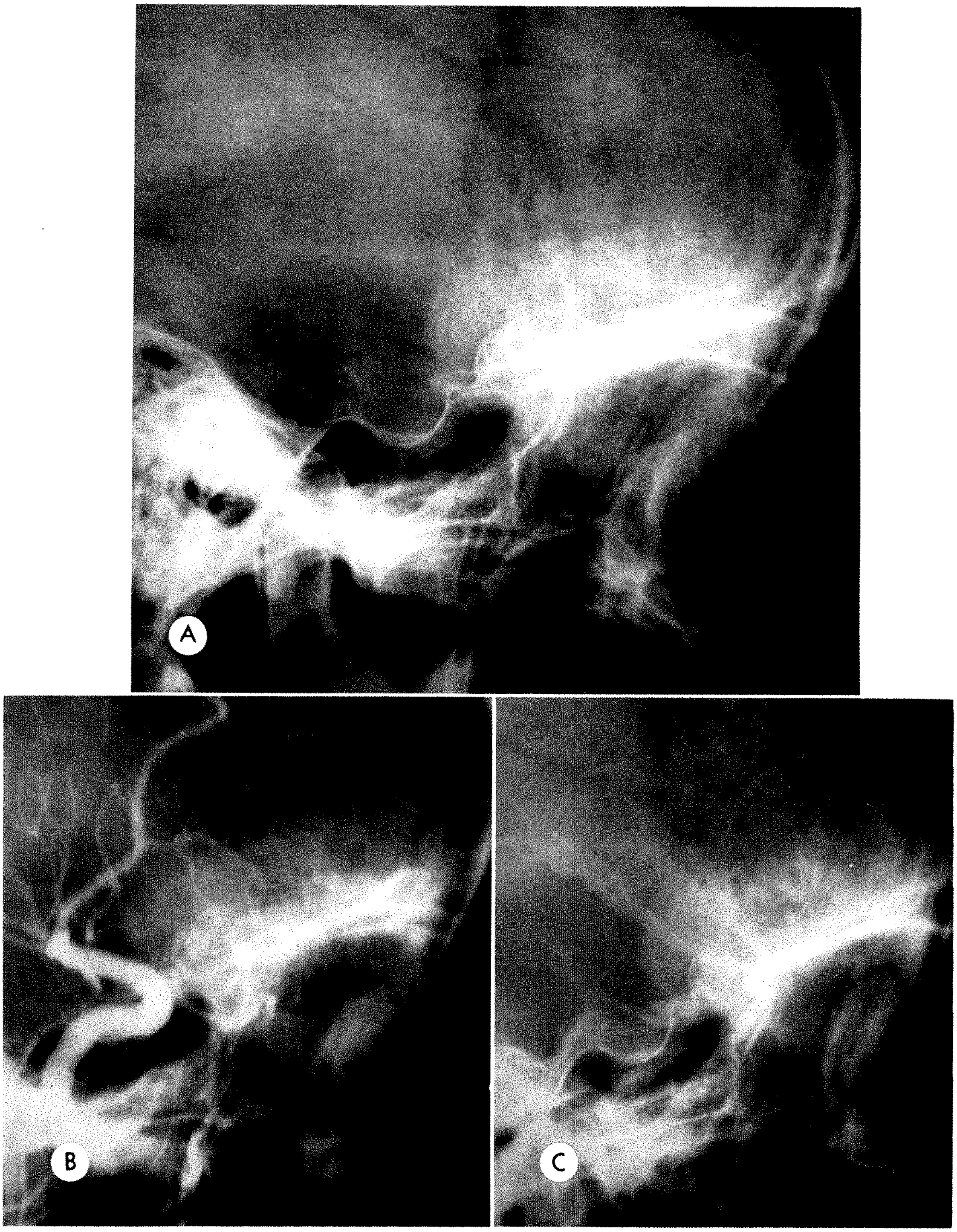

Fig. 1. (*A*) Plain roentgenogram showing diffuse thickening and hyperostosis in the olfactory groove area. (*B* and *C*) Angiograms show avascular meningioma.

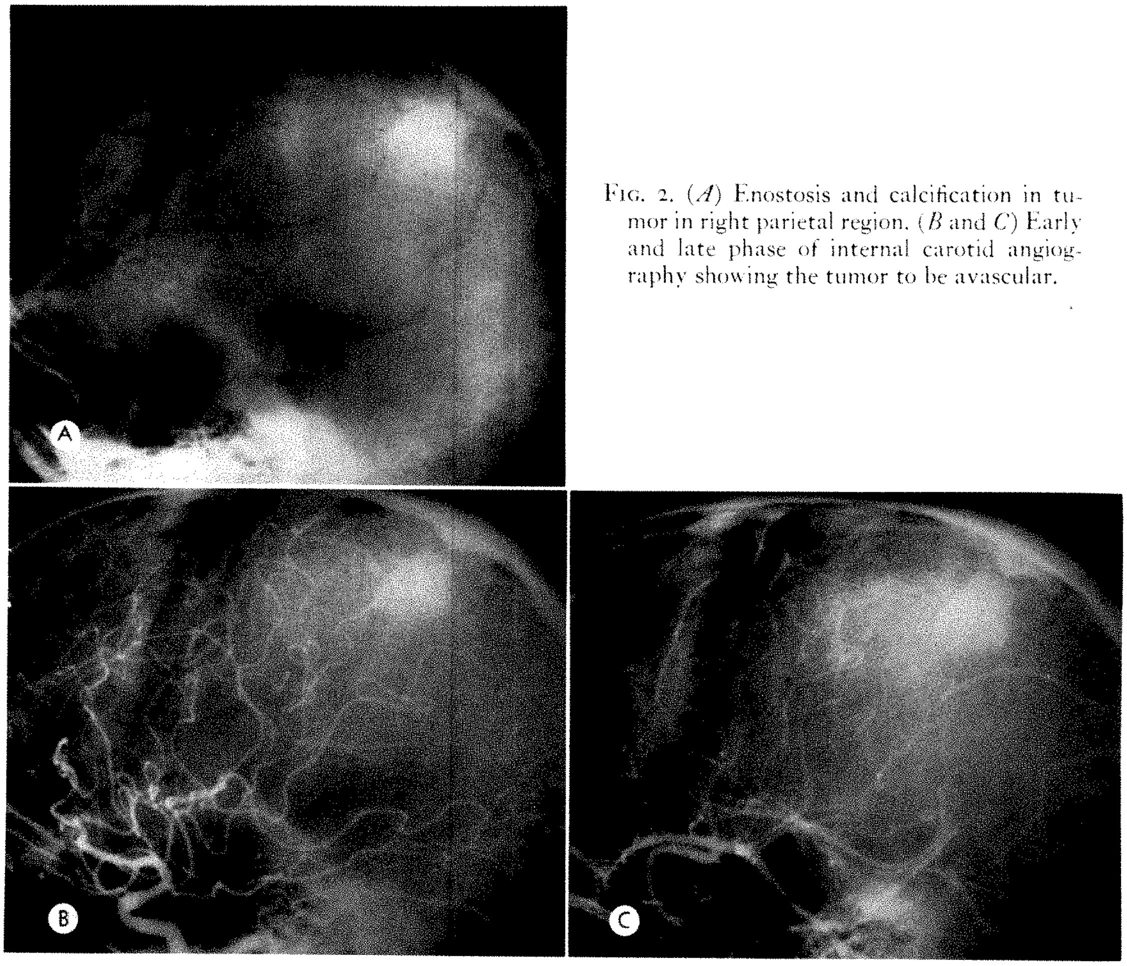

Fig. 2. (*A*) Enostosis and calcification in tumor in right parietal region. (*B* and *C*) Early and late phase of internal carotid angiography showing the tumor to be avascular.

cases between 1927 and 1948 in the files of the Department of Radiology showed a number with typical changes of hyperostosis with spicule formation.

Enostosis was noted in 23 cases (20.0 per cent). Bone thickening of the diploic space with occasional bone expansion was as frequent as hyperostosis, with 16 cases (13.9 per cent) presenting this finding. The size of the vascular channels in width and depth, unilateral as well as bilateral, was recorded and abnormalities were noted in 59 cases (51.0 per cent). Bone erosions of the inner table were observed in 14 cases (12.0 per cent). Calcification was only seen in 9 cases (7.8 per cent), a much lower figure than the usually reported incidence.

The arteriographic findings were recorded and are listed in Table IV. Seventy cases showed filling of the common carotid artery (60.8 per cent). In 38 cases (33.0 per

Table IV

Arteriographic Findings

1. External carotid filling	7 (6.0%)
Internal carotid filling	38 (33.0%)
Common carotid filling	70 (60.8%)
2. Shift of arterial vessels	109 (94.7%)
No shift of arterial vessels	6 (5.3%)
Sphenoid wing meningioma	1
Occipital meningioma	1
Anterior clinoid meningioma	1
Parietal meningioma	3
3. Avascular	59 (51.2%)
Abnormal vessels	73 (63.5%)
Blush	66 (57.4%)

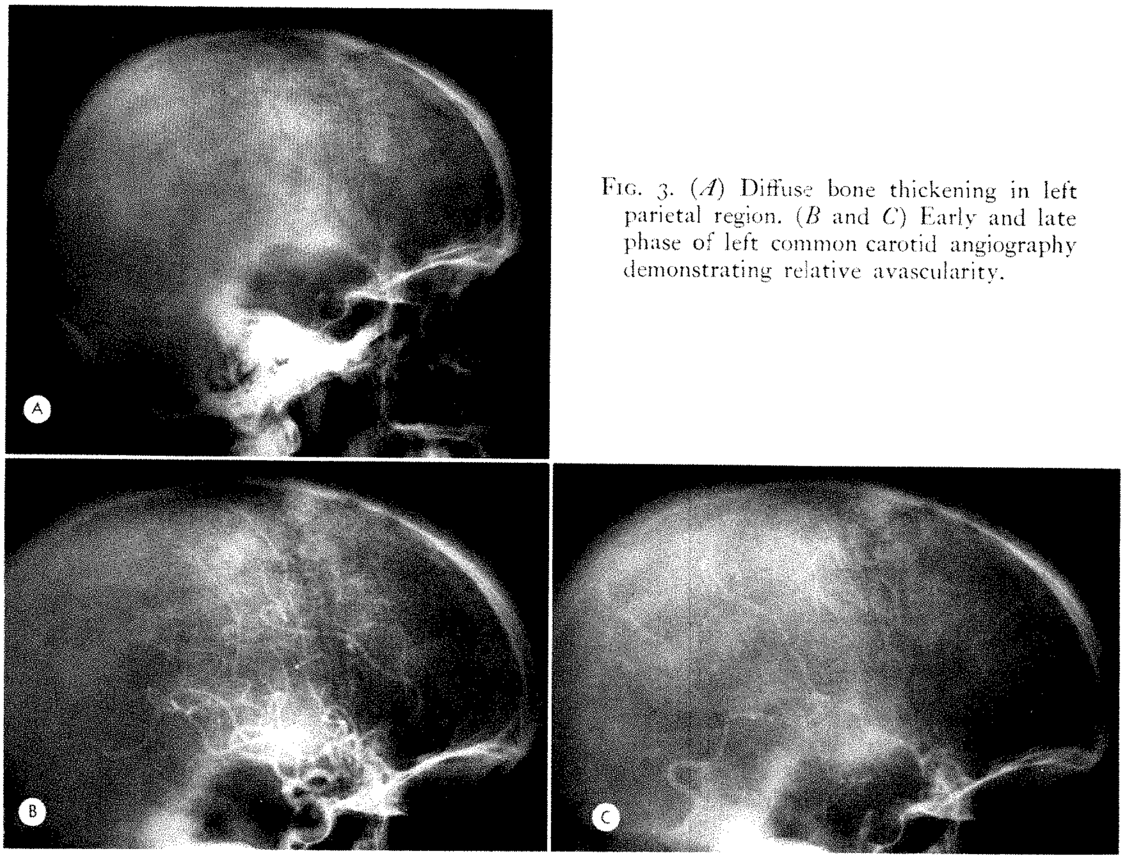

Fig. 3. (*A*) Diffuse bone thickening in left parietal region. (*B* and *C*) Early and late phase of left common carotid angiography demonstrating relative avascularity.

cent) the internal carotid artery only was visualized; in 7 cases (6.0 per cent) only the external carotid was filled. Shift of the intracranial branches of the internal carotid artery, in particular of the anterior and middle cerebral arteries, was seen in 109 cases (94.7 per cent). Six cases (5.3 per cent), with tumors of the inner third of the lesser wing of the sphenoid bone (1 case), anterior clinoid process (1 case), occipital lobe region (1 case), and parietal lobe region (3 cases), did not produce any recognizable shift of the intracranial vessels.

The vascularity of the meningiomas in this series was judged on angiograms by the presence of vascular opacity, abnormal vessels and complete or relative lack of vessels. Vascular opacity may be defined as a homogeneous tumor opacity with well demarcated borders, 66 cases (57.4 per cent). In this group may be included tumors showing general opacity with cloudy homogeneity.[6] The group with abnormal vessels showed distinct tumor vessels or vascular neoformations, 73 cases (63.5 per cent). This group may in some instances be associated with a moderate degree of tumor opacity. The avascular tumors showed an avascular area with crowding of displaced intracranial vessels around the tumor, 59 cases (51.2 per cent). Sometimes a few tumor vessels were faintly discernible.

Table v shows the correlation in this series between tumor vascularity and bone changes produced by the meningiomas. It was found that of 16 cases with hyperostosis 12 cases (75.0 per cent) appeared avascular on angiograms (Fig. 1, *A*, *B* and *C*). In only 4 cases (25.0 per cent) was a homogeneous blush present. In 7 instances (43.7 per cent) abnormal vessels were recognized. Out of 23 cases with enostosis, meningiomas showing no angiographic vascularity were present in 15 (65.2 per cent)

Table V

CORRELATION BETWEEN TUMOR VASCULARITY AND BONE CHANGES

	Hyperostosis 16 cases (13.9%)	Enostosis 23 cases (20.0%)	Diffuse Thickening 16 cases (13.9%)	Vascular Channels 59 cases (51.0%)	Bone Erosion 14 cases (12.0%)
Avascular	12 cases (75.0%)	15 cases (65.2%)	11 cases (68.7%)	17 cases (28.7%)	4 cases (28.5%)
Ring	No cases	1 case (4.3%)	2 cases (12.5%)	6 cases (10.1%)	2 cases (14.2%)
Hilus	1 case (6.2%)	8 cases (34.7%)	4 cases (25.0%)	25 cases (42.3%)	5 cases (35.7%)
Blush	4 cases (25.0%)	8 cases (34.9%)	4 cases (25.0%)	40 cases (68.0%)	10 cases (71.5%)
Abnormal vessels	7 cases (43.7%)	11 cases (47.8%)	7 cases (43.7%)	38 cases (67.7%)	10 cases (71.5%)

(Fig. 2, *A*, *B* and *C*). An over-all blush occurred in 8 of these cases (34.9 per cent) and abnormal vessels in 11 cases (47.8 per cent). As a rarity, a vascular ring (4.3 per cent) was observed in this subgroup. Diffuse bone thickening occurred in 16 cases. Of these, 11 (68.7 per cent) were avascular tumors (Fig. 3, *A*, *B* and *C*), 4 cases (25.0 per cent) showed a homogeneous blush and 7 cases (43.7 per cent) abnormal vessels. The vascular ring was seen in only 2 instances (12.5 per cent). Fifty-nine cases with prominent vascular channels could be linked with 17 (28.7 per cent) avascular meningiomas, but a blush occurred in 40 cases (68.0 per cent), (Fig. 4, *A*, *B* and *C*)

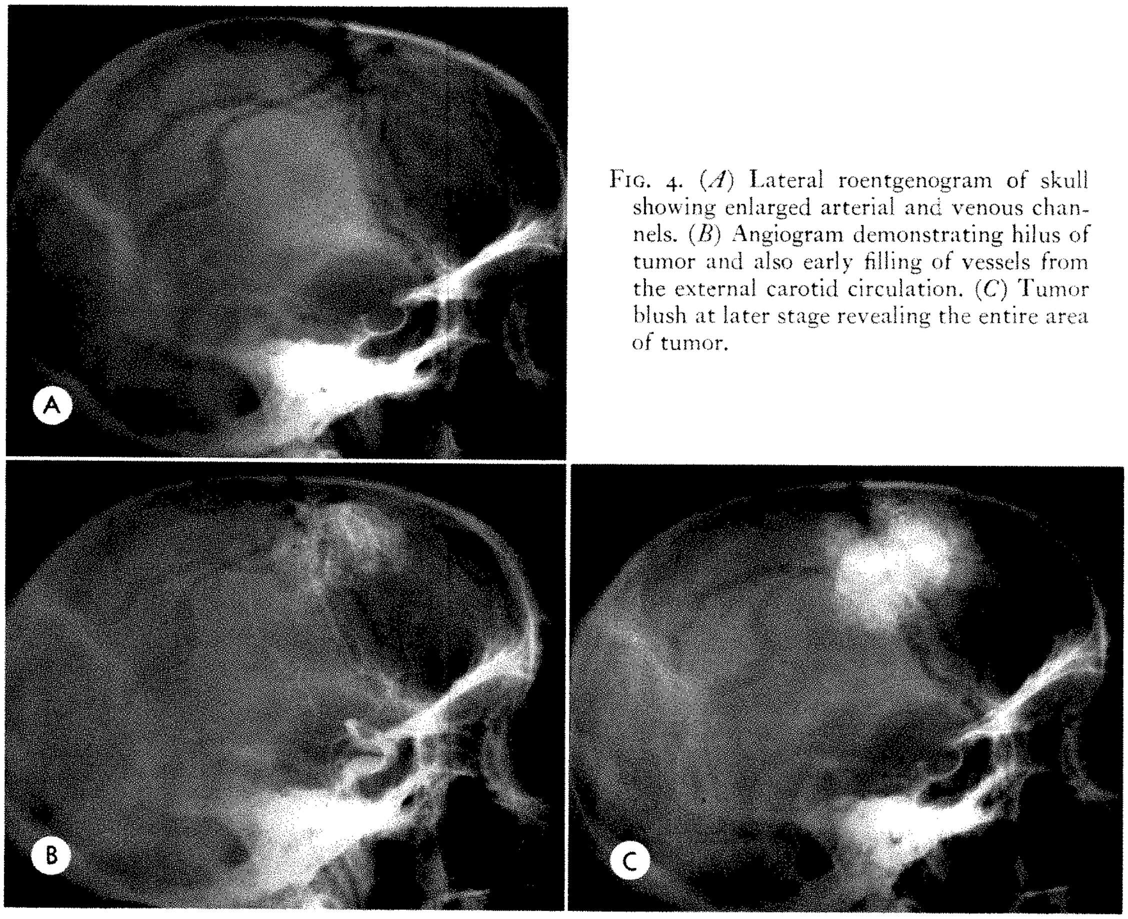

Fig. 4. (*A*) Lateral roentgenogram of skull showing enlarged arterial and venous channels. (*B*) Angiogram demonstrating hilus of tumor and also early filling of vessels from the external carotid circulation. (*C*) Tumor blush at later stage revealing the entire area of tumor.

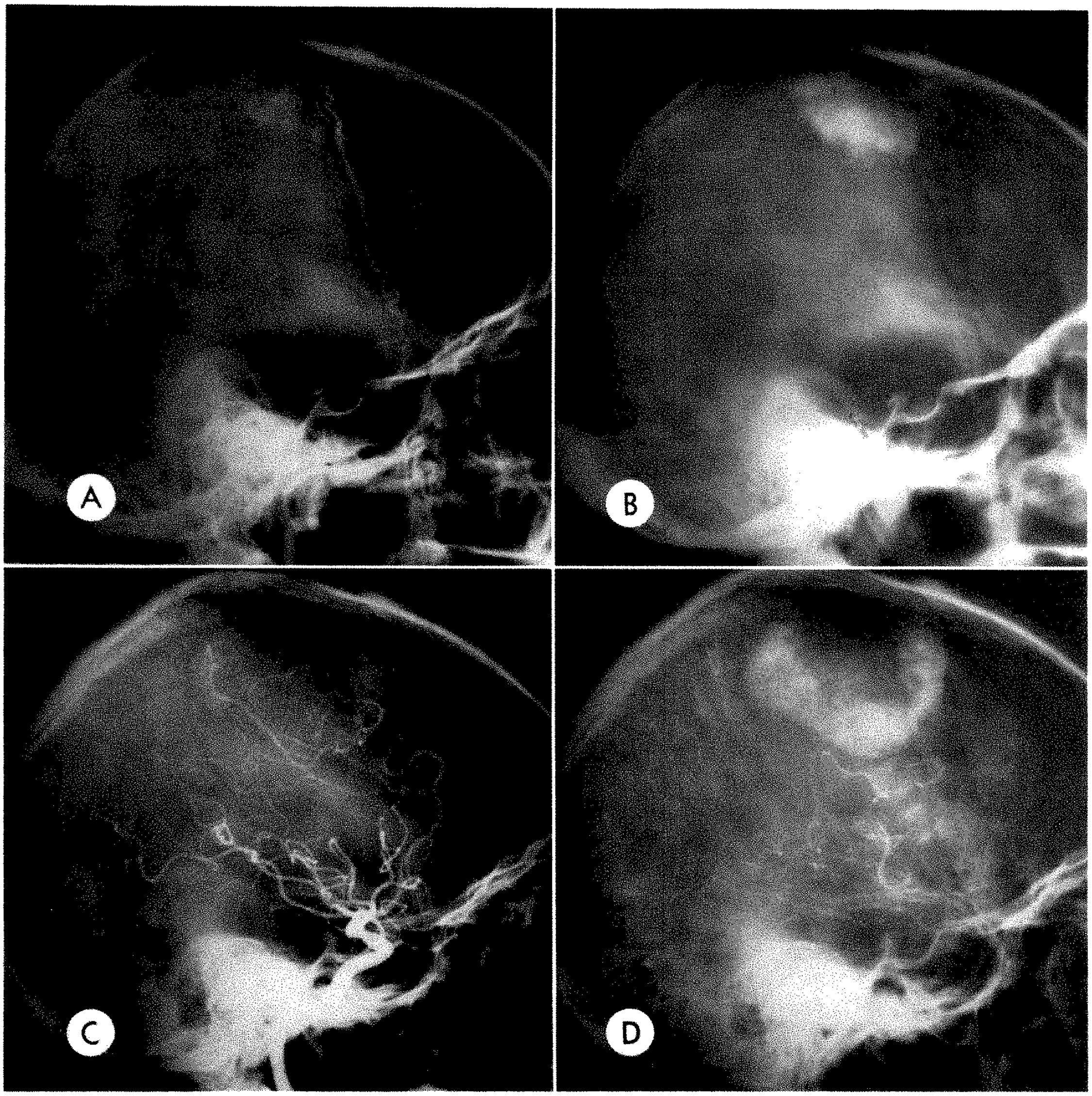

Fig. 5. (*A* and *B*) External carotid angiograms showing enlarged and tortuous meningeal vessels supplying hilus and central portion of tumor. (*C* and *D*) Internal carotid angiograms showing supply of the more peripheral part of the tumor from this source.

and abnormal vessels were noted in 38 cases (67.7 per cent) (Fig. 5, *A* and *B*). A vascular ring was present in 6 cases (10.1 per cent) (Fig. 5, *C* and *D*). The group of 14 cases with bone erosion showed vascular growths in only 4 instances (28.5 per cent). A homogeneous blush (Fig. 6, *A* and *B*) and abnormal vessels (Fig. 7, *A* and *B*) were seen in 10 instances (71.5 per cent). A vascular ring was present in 2 cases (14.2 per cent).

The operative findings and additional information were obtained from studies of the operation and case notes. The information obtained is listed in Table VI and can be compared with the roentgenologic results. Operative findings confirmed the presence of 13 cases with related hyperostosis; in 3 cases the roentgenologically observed hyperostoses were not commented upon in the operation records.

The enostoses verified at operation

amounted to 27 cases, 4 more than seen on the roentgenograms. In 11 instances the enostosis was considerable, while in the remainder it was small. Bone thickening was only noted in 4 cases at operation. The remaining 12 cases noted roentgenologically

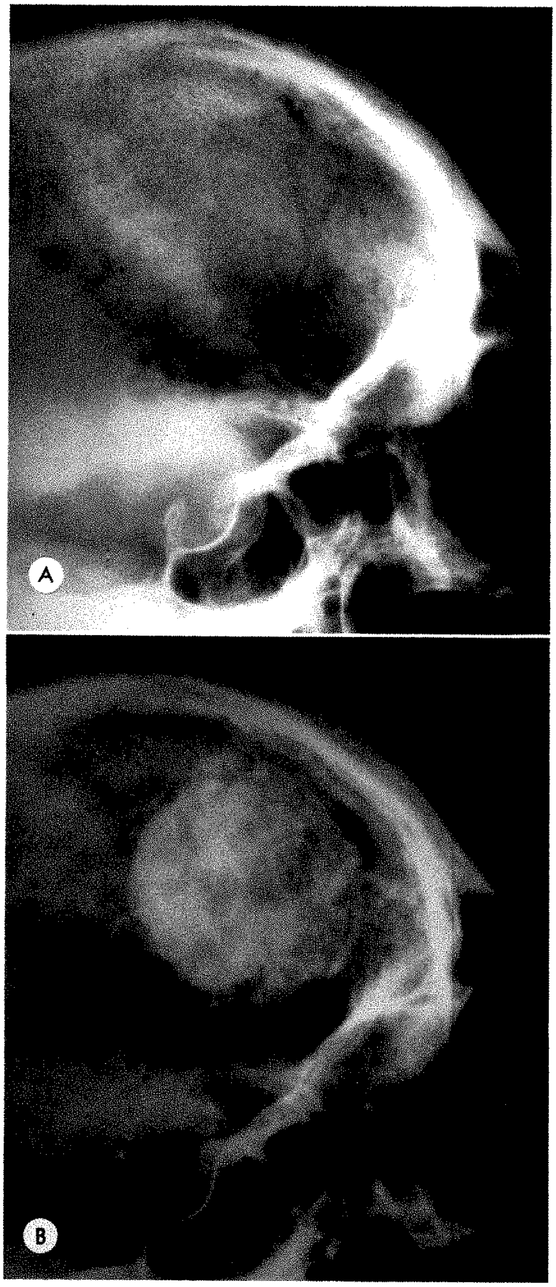

Fig. 6. (*A*) Extensive area of erosion demonstrated in left frontal bone. (*B*) Angiogram shows typical meningioma "blush."

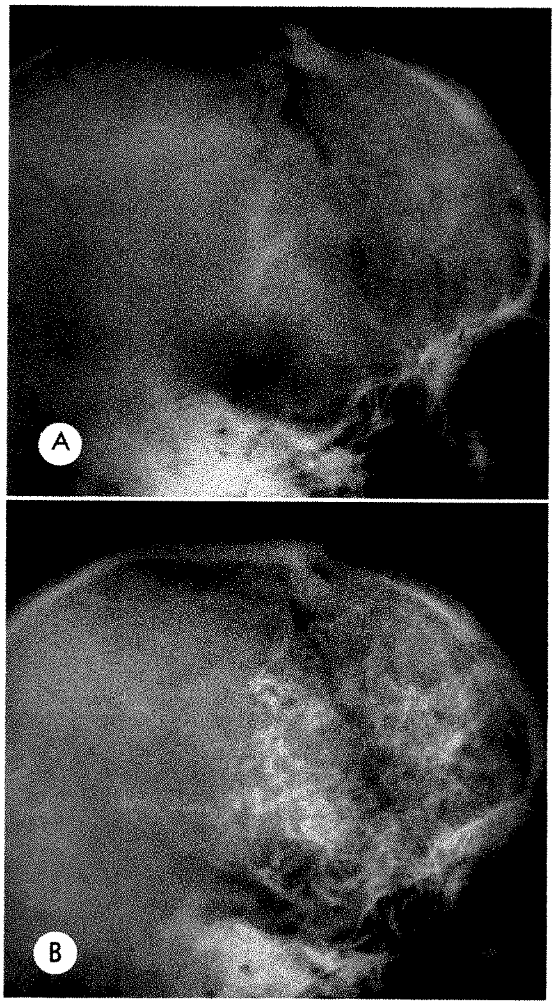

Fig. 7. (*A*) Gross bony erosion in the left frontal region. (*B*) Highly vascular meningioma with extensive abnormal vessels.

Table VI

OPERATIVE REPORTS

	Roentgenologic Findings	
	Confirmed	Unconfirmed
Enostosis		
Small	16	—
Large	11	—
Hyperostosis	13	3
Bone thickening	4	12
Bone erosion	7	7
Sagittal sinus invasion noted		26
Invasion of dural structures noted		91

were not commented upon at operation. Bone erosion was observed at operation in only 7 cases. The other 7 cases of erosion observed roentgenologically were not noted in the operative report. Vascular channels in the presence of meningiomas have only been commented upon very sporadically in the operative reports. It is assumed that this finding is not always recorded and it is therefore omitted from our series.

Out of 115 cases of meningioma, 26 showed invasion of the superior or inferior sagittal sinus. In 2 instances the involvement was questionable. There was no operative record of the amount and extent of obstruction in the sinus. Invasion of the dural structures by meningiomas was frequently found in this series. In 91 cases there was invasion of either the peripheral dura and/or the falx or tentorium. In 4 cases invasion was considered to be questionable. The surgical reports varied somewhat in their detail and therefore only an incomplete over-all picture could be obtained.

Disparity between the operative records and the roentgenologic data is possibly explained by the differing surgical records. The entire series was histologically reviewed by one of us (M.D.) to reassess the pathologic findings. Of the 115 cases, 4 could not be examined for various reasons, and in 9 cases the relevant pathologic material was not available. Therefore only 102 cases were reviewed histologically. The review was essentially confined to a diagnosis of the tumor type and a survey of the vascularity in each case was made. The assessment of vascularity was largely subjective, no attempt being made to measure the caliber of vessels or to accurately account for the number of vessels per microscopic field. It is felt that, since all tumors were assessed by a single observer, the estimate of relative vascularity should be valid.

On the basis of relative vascularity the tumors were classified in 4 groups: (1) +, avascular; (2) ++, moderately avascular; (3) +++, moderately vascular; and (4) ++++, very vascular.

For comparison with the roentgenologic study it was felt desirable to restrict classification to 3 categories (+, ++, +++). It seemed reasonable to combine the first 2 groups (+, ++) into a single group since the difference in vascularity between these 2 groups is considerably less than that between groups 3 and 4. Fourteen cases of meningioma were of the angioblastic type (++++) (Fig. 8*A*); 55 cases showed moderate vascularization (+++) (Fig. 8*B*); only 4 cases were regarded as avascular (Fig. 8*C*), these being fibroblastic in type, while 29 cases were considered to be relatively avascular meningiomas. During the histologic review an attempt to classify the tumors according to whether they were vascularized by predominantly small or large vessels was also made. It was found that 14 cases had predominantly large vessels and 32 cases mainly small vessels, while in the remainder both small and large vessels were present in approximately equivalent numbers (Table VII).

Of the 102 cases histologic examination showed calcification in 16 instances (about 15 per cent) as compared with 9 calcifications out of 115 cases (7.8 per cent) found on roentgenograms. One case of meningioma was found to be associated with a glioblastoma multiforme.

TABLE VII

PATHOLOGY FINDINGS

Clinical Cases	115
Histologic Reassessment Possible	102
14	cases had ++++ vascularity
55	cases had +++ vascularity
29	cases had ++ vascularity
4	cases had + vascularity
56	tumors with small and large vessels
32	tumors with small vessels predominating
14	tumors with large vessels predominating
16	cases showed histologic calcification
1	case of meningioma was associated with a glioblastoma

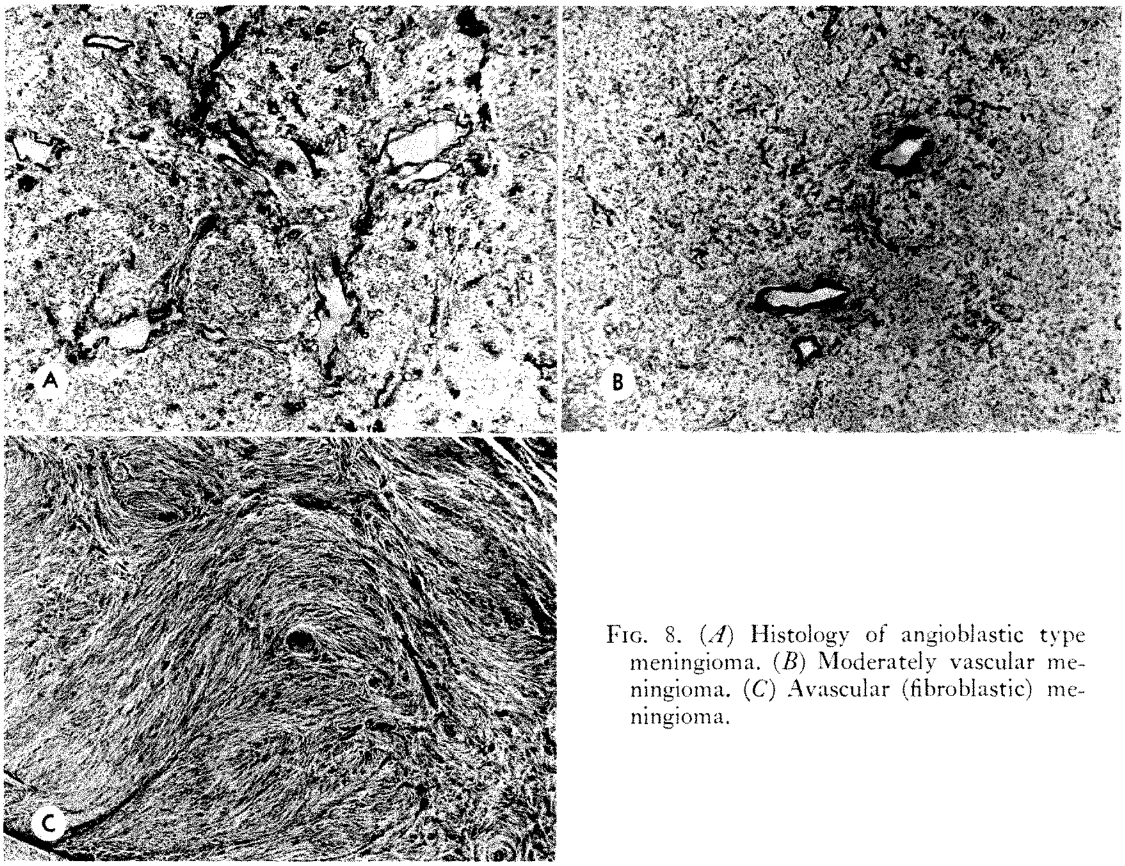

Fig. 8. (*A*) Histology of angioblastic type meningioma. (*B*) Moderately vascular meningioma. (*C*) Avascular (fibroblastic) meningioma.

DISCUSSION

Many investigators have commented upon the etiology of hyperostosis associated with meningiomas. Numerous publications have dealt with increased vascularity in the diploic spaces and vascular grooves caused by hypertrophy of the branches of the external carotid artery. Osteoblastic reaction of bone due to meningeal tumors is still, in spite of many theories, a matter of contention. In the last decade more modern concepts of tumor circulation have been put forward to increase understanding of the nature of the meningiomas. The authors have attempted to correlate the appearance of tumor circulation seen in the angiogram with the bony changes which are often associated with meningeal tumors. This investigation was intended to determine which type of meningioma might be expected when various bone changes were seen on the plain skull roentgenograms.

This series shows that the incidence of avascularity in the presence of hyperostosis, enostosis and diffuse bone thickening lies above 65.2 per cent, while that of increased vascularity is below 47.8 per cent. The cases with increased vascular channels and bone erosion show an incidence of avascularity below 28.7 per cent. The vascularity of these latter groups is above 67.7 per cent. These findings demonstrate the relatively high incidence of hyperostosis, enostosis and bone thickening and the relatively low incidence of vascular bone channels and erosion associated with avascular meningiomas. A high incidence of prominent vascular channels and bone erosion was observed in the presence of a vascular type of meningioma, which is less commonly associated with hyperostosis, bone thickening and enostosis. It can therefore be stated that where hyperostosis, enostosis, or bone thickening is seen on the roentgenogram, a relatively avascular meningioma may be expected and that in cases with increased vascular channels and bone erosion, a vascular meningioma may be encountered at operation.

The changes noted on plain roentgenograms in this series proved to be important. Demineralization of the floor of the sella turcica and the posterior clinoid processes was evaluated by the criteria used by Mahmoud (1958) which were found to be useful and accurate. The present series showed positive signs in 63.5 per cent of cases. Pineal shift was noted in 34.8 per cent of the 115 cases, a much higher incidence than that noted by Jacobson *et al.*[6] The incidence of calcification seen on the plain roentgenogram was, however, much lower than described in other series (7.8 per cent). In this series there was a slightly higher incidence in females than in males; these findings coincide with those of Horrax.[5] The highest local incidence of meningiomas was found to be in the parasagittal location (67.6 per cent) as against 73 per cent reported by Jacobson *et al.*[6] Increased vascular channels were noted in 51 per cent which is comparable with the 50 per cent incidence found by Elsberg and Schwartz[4] in their series.

The tumors were divided into 3 roentgenologic groups: vascular (homogeneous opacification); those showing abnormal vessels with an associated slight tumor blush; and those with complete or relative avascularity. These findings were compared and correlated with the histology in each case. In about 89.3 per cent the histologic vascularity of the tumor showed correlation with the degree of vascularity expected from roentgenographic findings. The remaining cases (10.7 per cent) showed lack of correlation of vascularity, assessed by roentgenologic and histologic methods, probably due to inadequate sampling of the total specimen. Usually, only a small portion of the tumor is sectioned, and, where vascularity differs from area to area, selection of a particular area will determine the apparent vascularity. On the other hand, lack of correlation of the roentgenologic findings with the histologic specimen may be due to the fact that only one, or a few afferent vessels of the dural supply of a meningioma may be injected, and, therefore, a relative avascular zone seen on the arteriogram may be due to nonfilling of the main supplying vessel. It was observed by Wickbom[15] and Lindgren[9] that in the case of selective injection of the external carotid artery, the central portion, and, by internal carotid injection, the peripheral portion of the tumor may be demarcated (Fig. 5, *A–D*). In some cases only a segment of the tumor may be outlined, instead of the center part with selective arterial punctures. The ring type tumor opacification was observed in 11 of our cases.

Correlation of the operative findings in these cases with the roentgenologic series demonstrates the fact that the incidence of enostosis visible at operation is slightly higher than that observed on the skull roentgenograms. Four cases of enostosis found at operation were not demonstrated roentgenologically. This is to be explained by the fact that the enostosis was small and a tangential view of the involved area was not available for interpretation. In 3 cases, hyperostosis, seen in the roentgenogram, was not recorded in the operation report, possibly due to oversight, since roentgenographically noted bone thickening, *i.e.*, sclerosis of the diploic spaces, was infrequently commented upon at operation. Bone erosion, much more frequently seen roentgenographically, was only noted at operation in 5 cases as against 14 such observations on the roentgenograms. It is believed that porosity of the inner table due to bone erosion is more readily demonstrable roentgenographically than at operation. An attempt was made to correlate the hilus of the meningioma, demonstrated very clearly in many instances on the roentgenogram, with the operative findings. Unfortunately, many of the surgical reports failed to record details of this finding. It was therefore decided to omit details of this appearance. The operative records revealed that invasion of the superior or inferior sagittal sinus occurred in 26 cases. Invasion of the dura was encountered in 91 out of 115 cases.

Bone changes seen on the roentgenogram could not be correlated with histologic changes in the bone specimens because of inadequate records.

SUMMARY

A short review of the literature concerning meningiomas, relevant to the study under consideration, is given.

The vascularity of 115 meningiomas was assessed in relation to associated bone changes in the skull. It was found that a relatively avascular meningioma is usually associated with hyperostosis, enostosis and bone thickening, while a vascular meningioma is often associated with increased vascular bone channels and bone erosion.

The changes on plain skull roentgenograms in regard to the sella turcica and pineal gland shift in the presence of meningiomas were observed and recorded.

The sex incidence in patients with meningiomas and the incidence of meningioma location were determined and compared with similar findings in the literature. The operative records were reviewed and compared with the roentgen findings.

The histology of the cases was studied and classification as to vascularity was carried out. This was considered in the light of the roentgenologic findings.

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LYMPHANGIOGRAPHY IN OBSTRUCTION*

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LYMPHAGIOGRAPHY is a practical approach to the study of anatomy, physiology, and pathology of a system which until recently was not amenable to direct roentgenographic visualization.[3,8,11] Our method of lymphangiography follows that described by other authors.[1,2,4,9] The indications for its use are as follows: (1) study of chylothorax, chyloperitoneum, and chyluria; (2) evaluation of lymphadenitis; (3) determination of the extent of metastatic or neoplastic involvement of lymph nodes and to some degree the pathologic nature of this involvement; (4) as a source of preoperative planning of lymph node dissection and as a monitor in the operating room of the completeness of the surgical removal; (5) proper anatomic placement of radiation ports; and (6) study of lymphatic obstruction. This paper is concerned with the manifestations resulting from obstruction.[5,6]

The lymphatic system responds to impairment of its natural pathways of drainage in different ways. There may be simply an increase in the number of vessels coursing along the proper pathways, or accompanying this increase, there may be dilatation of the vessels. Dilatation has also been seen without an increase in the number of channels. Some patients show a massive filling of the skin lymphatic vessels and formation of collateral circulation at a more peripheral level. This has been referred to as dermal backflow. In an obstructed extremity any one of these changes may occur locally, not necessarily indicating the level of the mechanical block. Lymphangiograms will show these changes immediately after the completion of the injection. A factor of greatest importance is that 12 and 24 hour delayed lymphangiograms continue to show these abnormalities. Indeed contrast material may remain in these abnormal channels for days if the obstruction is severe, whereas in normal unobstructed channels, the medium is emptied in 24 hours.

The pelvis and abdomen show great hypertrophy of the lymph vessel network. The pelvic vessels tend to course toward the mid-line and anastomose with the internal pelvic drainage system; this is not normally seen after injection into the feet. In the abdomen the normal lymphatic vessels stay close to the vertebral column as they form the para-aortic chain. In obstruction, however, there may be collateral branching outward toward the kidney areas. This was dramatically demonstrated recently in a chyluria patient in whom a chylous fistula was visualized between the lymphatic system and the urinary tract on lymphangiograms.[7]

Below are some illustrative cases in which lymphangiography has proved to be a valuable procedure.

ILLUSTRATIVE CASES

CASE I. This 34 year old man entered the hospital with the chief complaint of intermittent right leg swelling for a period of 20 years. This had become more persistent in the preceding few years. The past history was significant in that approximately 24 years prior to admission, he probably had filariasis. On physical examination the right lower leg was edematous with thickened skin.

Lymphangiography revealed an increased number of vessels, some extending quite peripherally (Fig. 1). The caliber of the vessels was normal. On a 24 hour lymphangiogram an abnormal network of vessels was still visualized in the calf area. (Fig. 2).

CASE II. This 78 year old woman entered the hospital with the diagnosis of carcinoma of the vulva. This was surgically removed. The inguinal lymph nodes were slightly enlarged bilaterally. Three months later a left groin dissection was performed. This was followed in 1 month by a right groin dissection. The lymph nodes contained tumor bilaterally. Following the groin dissections the patient developed episodic swelling of both thighs and to a lesser degree of both lower legs. The skin remained normal in texture. The edema was never incapacitating and responded well to rest and leg elevation.

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Lymphangiography was performed 1 year following the dissections. The vessels in the lower leg were increased in number and showed definite areas of dilatation and beading (Fig. 3). The local areas of dilatation in the lower thigh were more marked on a 24 hour follow-up lymphangiogram (Fig. 4). In the inner aspects of both thighs, where the edema was most persistent, there was massive filling of the skin lymphatic vessels (Fig. 5).

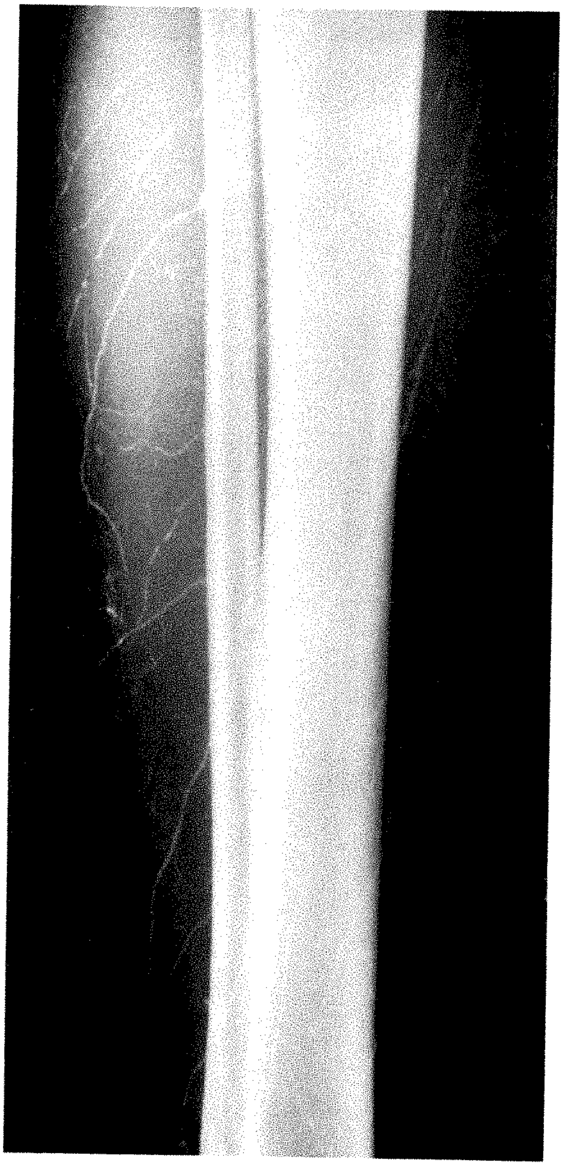

Fig. 1. Case I. A lymphangiogram shows an increased number of vessels, some extending rather peripherally. The caliber of the vessels is quite normal.

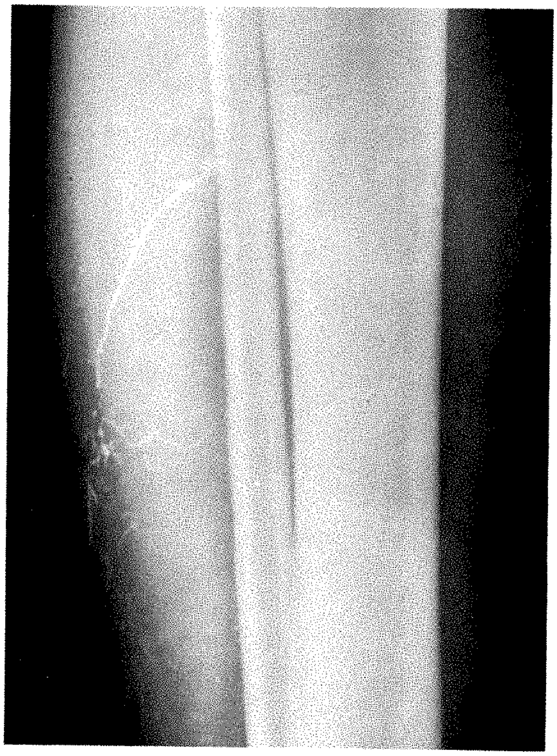

Fig. 2. Case I. A 24 hour lymphangiogram shows an abnormal network of vessels still visualized in the calf area.

Case III. This 58 year old woman had a subtotal gastrectomy for carcinoma of the stomach. At operation, metastases were noted in the abdominal cavity, liver, mesentery and pelvis. In the 2 years following operation, she developed recurrent chylous pleural effusion.

A lymphangiogram made 2 years after operation showed a marked increase in the number of vessels with dilatation and dermal backflow in both infrainguinal areas (Fig. 6). On the 48 hour follow-up lymphangiograms changes were still dramatically seen. In the pelvis, contrast material had dissected towards the midline to anastomoses with the internal pelvic drainage system (Fig. 7). In the abdomen, there was flow of contrast material laterally towards the renal

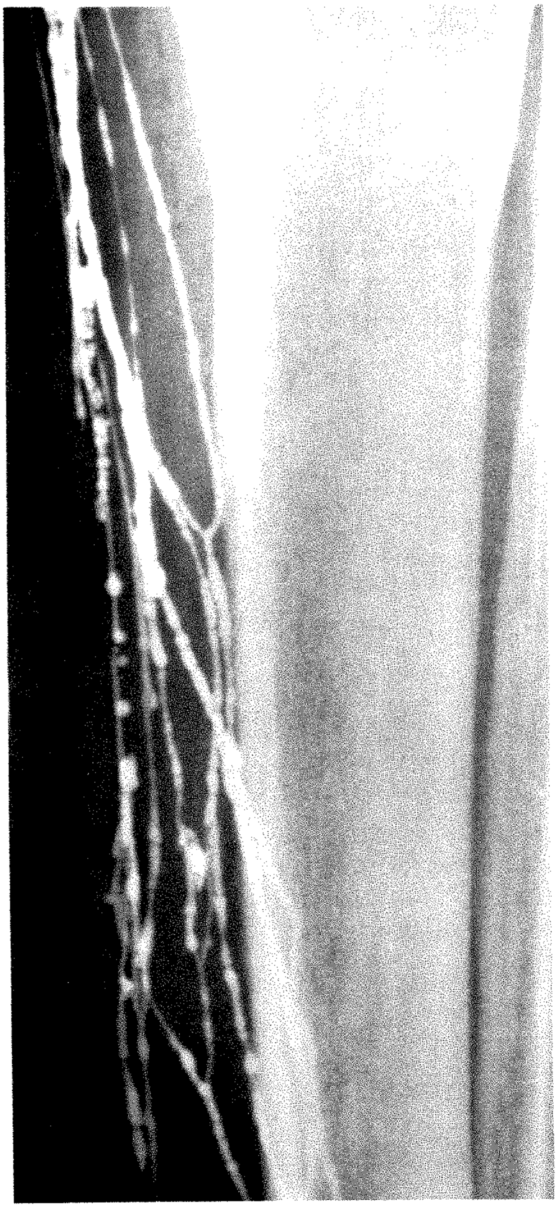

Fig. 3. Case ii. A lymphangiogram shows an increased number of vessels in the lower leg and definite areas of dilatation and beading.

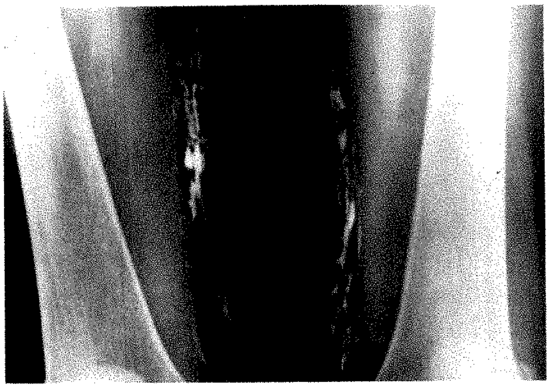

Fig. 4. Case ii. The local areas of dilatation are more marked in the lower thigh on a 24 hour follow-up lymphangiogram.

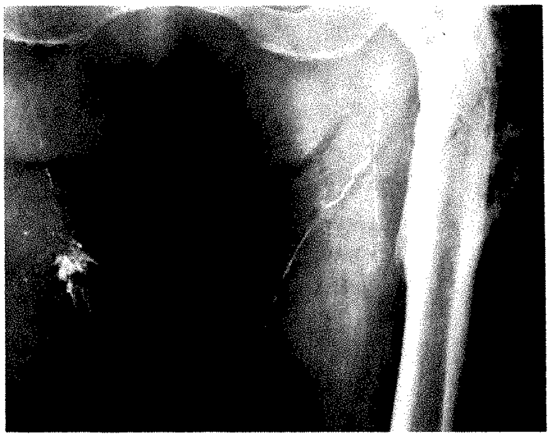

Fig. 5. Case ii. In the inner aspects of both thighs, where the edema was most persistent, there is massive filling of the skin lymphatic vessels.

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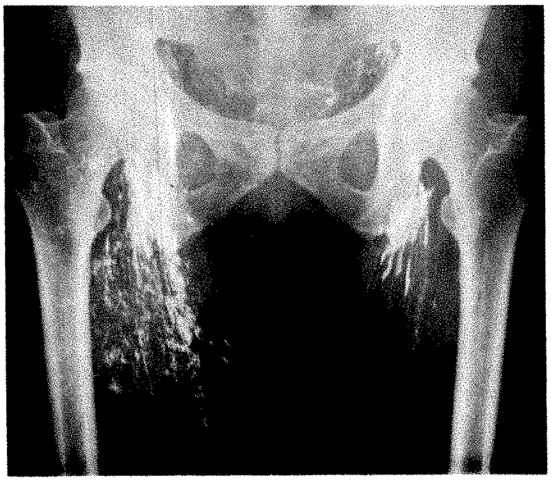
Fig. 6. Case iii. A lymphangiogram shows the marked increase in the number of vessels with dilatation and dermal backflow in both infra-inguinal areas.



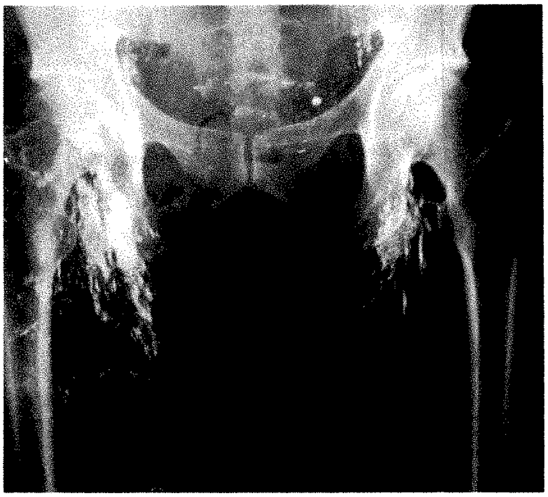


Fig. 7. Case III. A 48 hour follow-up lymphangiogram of the pelvis shows that contrast material has dissected towards the midline to anastomoses with the internal pelvic drainage system.

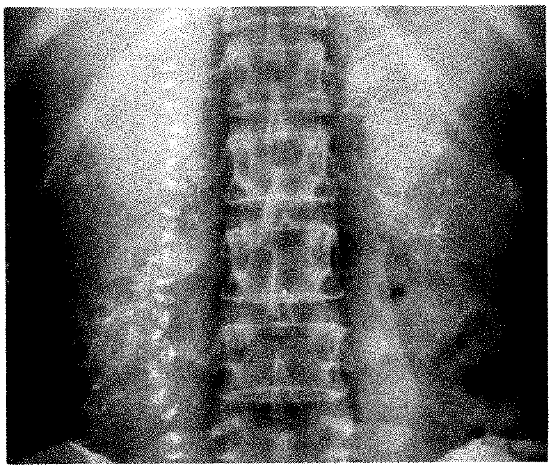


Fig. 8. Case III. A 48 hour lymphangiogram of the abdomen shows a flow of contrast material laterally towards the renal and peripheral retroperitoneal lymphatic vessels.

and peripheral retroperitoneal lymphatic vessels (Fig. 8).

SUMMARY

The different responses of the lymphatic vessels to obstruction as revealed by lymphangiography are discussed and illustrative examples are given. These changes when interpreted will often explain the clinical picture.

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ANGIOGRAPHY USING DIRECT ROENTGENOGRAPHIC MAGNIFICATION IN MAN*

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INCREASED interest in cardiovascular diagnostic and therapeutic techniques has enhanced the need for refinements in the techniques of angiography to yield better angiograms, with finer detail and greater clarity and definition than ordinary techniques can provide. A roentgenologic technique has been available for approximately a decade[7] by which the roentgen image is magnified directly, with preservation of fine detail. This is accomplished by using the ultra-fine focal spot of the rotating-anode roentgen tube as the roentgen-ray source, and by altering the usual tube-object-film distance relationships so that the tube is closer to and the film farther from the object. A magnified image with enhanced detail may thus be obtained. Use of this technique thus far has been limited to studies involving bones, joints, soft tissue calcifications, and the lung parenchyma. Recently, it has been applied with success in angiography in the experimental animal, to delineate cerebral, coronary, renal and peripheral vessels.[4,5] This report details the initial promising studies in man.

METHOD

The subject or part to be magnified was positioned on a horizontal radiolucent portable table-top * supported at either end by fixed or movable supports, and elevated approximately 20 inches above the film. Scissors-type automobile jacks could be adapted admirably for this purpose (Fig. 1, *A* and *B*). The roentgen tube was positioned at a distance of 40 inches from the film, providing 2× magnification.

The fine (0.3 mm.) focal spot of either the standard double-focus rotating-anode roentgen tube** or a specially constructed roentgen tube† was used in these studies. Film changers included a manually-operated tunnel cassette changer,[6] an automatically operated long-cassette changer‡ or the standard single-plane Schönander film changer. Roentgenographic films used were par speed du Pont or Ansco film, with par speed intensifying screens. With the Schönander apparatus, the standard grid (60 lines to the inch) was used; however, with the automatic long-cassette changer, a fine-line grid, 110 lines to the inch, was employed.

A control roentgenogram was taken for position and technique. Using the Machlett tube, which permits a maximum of 20 ma. of current, exposure times varied from ⅕th to ½ second for peripheral angiograms, and up to 6 seconds for abdominal aortograms; the kv.p. depended upon the part being examined. The specially constructed Dunlee tube permitted pulmonary angiograms to be made using the Schönander film changer at ⅕th of a second, 100 ma., 74–88 kv.p.

For peripheral arteriograms, an 18 gauge thin-walled arterial needle was inserted well up into the femoral or brachial artery in a retrograde direction percutaneously, and to this was attached a short length of plastic tubing with adapters for needle and syringe.

Circulation time to the extremities (hands and feet or the popliteal area) was

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* Schönander-Elema.

** Machlett Laboratories, Inc., Springdale, Connecticut.
† Dunlee Corporation, Bellwood, Illinois.
‡ Grafax Corporation, New York, New York.

* From the Cardiopulmonary Research Laboratory and the Radiology Service, Veterans Administration Hospital, Oteen, North Carolina.

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† Chief, Surgical Service, Veterans Administration.
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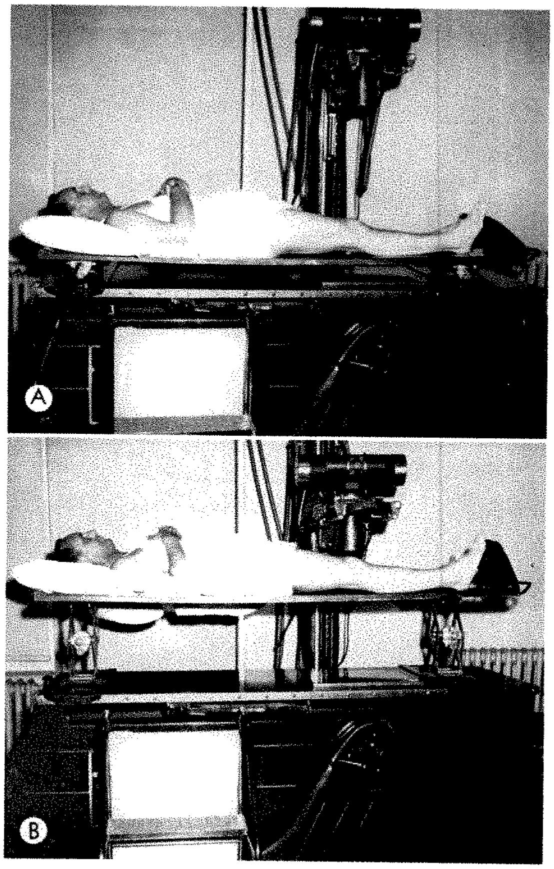

Fig. 1. (*A*) Arrangement of roentgen tube, patient, and roentgen-ray cassette to produce the arteriogram in Figure 3. Patient placed on radiolucent table top supported by specially adapted scissors-type automobile jacks, which initially are in the down position. (*B*) The table top bearing the patient has been elevated to a height of approximately 18 inches above the cassette, giving a target-film distance which is twice the target-object distance. In practice, the roentgenographic film is in a rapid film changer of the tunnel type, or in an automatic film changer (see text).

determined next, using radioactive iodinated serum albumin (RISA) with a 1 inch scintillation detector* positioned directly over the field of interest. RISA in a quantity of 40 to 100 μc in a 3 to 5 cc. volume of saline was placed into the plastic tubing; it was then rapidly injected into the artery by injecting a bolus of 20 cc. of saline contained in a hand-held syringe attached to the tubing. The initial peak of the curve recorded by a direct-writing recorder gave an estimate of the interval of time elapsing between the injection of the RISA into the brachial or femoral artery, and its appearance at the periphery. This was used to determine the time interval to be observed between the injection of radiopaque medium and the beginning of roentgenographic exposures.

For the lower extremities, including the feet, sodium and methylglucamine diatrizoates, 60 per cent,** in 30 to 50 cc. doses was injected; for the angiograms of the small vessels of the hand, 15 cc. of a solution of 50 per cent diatrizoate sodium† was used, diluted to a 25 per cent solution using an equal volume of the patient's own blood, 3 to 5 minutes after an intra-arterial injection of 50 mg. of tolazoline hydrochloride‡ in 10 cc. of saline. Most of these injections were made manually.

For pulmonary angiography and intravenous abdominal aortography, the standard technique was used of inserting a large-bore NIH catheter into the right atrium under fluoroscopic guidance. Circulation time to the abdominal aorta (but not to the pulmonary vessels) was determined by injecting as little as 16 μc of RISA into the right atrium rapidly while the scintillation detector was held over the epigastrium midway between the xiphoid process and the umbilicus. The radiopaque medium used was 60 to 100 cc. of sodium diprotrizoate and diatrizoate§ injected with a Gidlund high pressure manually-operated syringe.

RESULTS

Angiograms using direct roentgenographic magnification were obtained in 17 patients thus far. In 7, the extremities were the subject of study; in 5, abdominal or renal arteriograms were attempted; and in 4, pulmonary angiograms were made. A single cerebral angiogram was attempted in one patient.

The greatest success was obtained in

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* Nuclear-Chicago Corporation, Des Plaines, Illinois.

** Renografin.

† Hypaque.

‡ Priscoline.

§ Ditriokon.

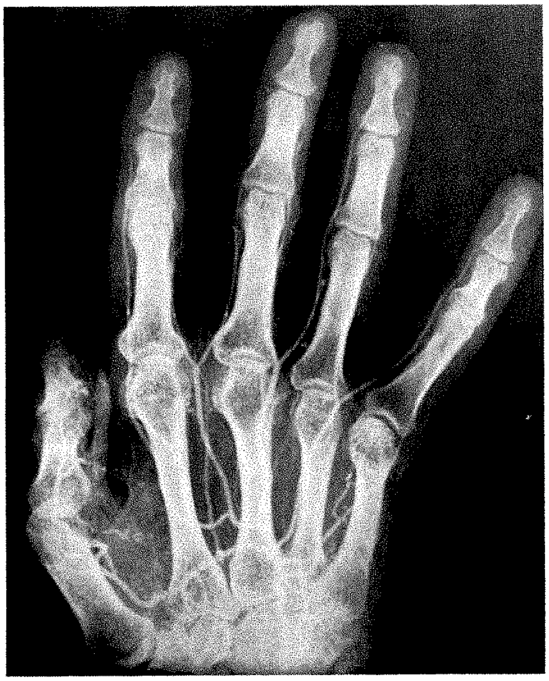

FIG. 2. Arteriogram obtained using direct roentgenographic magnification of the left hand of a patient with bilateral below knee amputations for Buerger's disease. Occlusion of the distal segments of the digital arteries to the index and middle fingers is demonstrable.

peripheral angiography, as would be expected from the limitations on the technical factors which were imposed by the characteristics of the fine focal spot of the roentgen tube used. Details of digital arteries and the vascular tufts at the ends of the fingers could be visualized in both the patients in whom the technique was applied (Fig. 2). In one patient with a soft tissue tumor of the lower leg, very fine vascular detail could be made out with clarity (Fig. 3). The pulmonary angiograms also showed great promise, with excellent visualization of the fine vascularity of the pulmonary parenchyma (Fig. 4). This was also true if the ultra-fine focal spot of the special roentgen tube was used even without magnification. The angiograms attempted of the abdominal vessels and of the cerebrum left much to be desired, since the greater penetration necessary could not be achieved with very short exposures, and longer exposures allowed motion to produce blurring.

DISCUSSION

In the continuing clinical study of diseases affecting the small vessels of the coronary, pulmonary, renal, cerebral, and peripheral circulation, it would seem to be invaluable to have available a technique of angiography which could provide clear and detailed visualization of vessels down to a diameter of 100 μ or less. Such a technique has been explored clinically by Takahashi,[3]

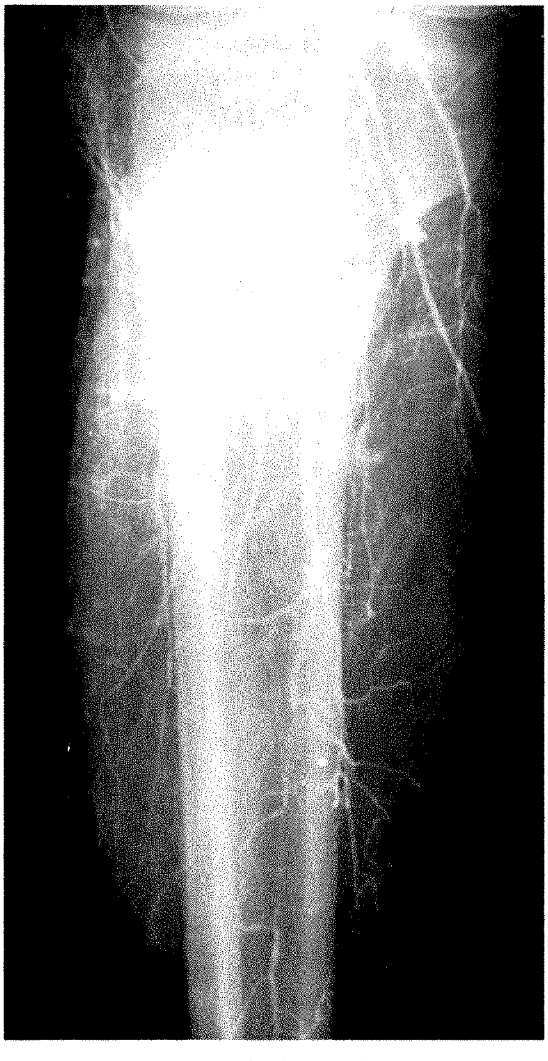

FIG. 3. Arteriogram obtained using direct roentgenographic magnification of an atypical myxoma involving the anterolateral aspect of the right leg.

and is available for experimental animals.[4,5] The limitation imposed by the small total milliamperes tolerated by targets of ultrafine focal spot size necessitates longer exposures than are desirable. This requires momentary circulatory arrest for optimal results in coronary arteriography, and balloon occlusion of the suprarenal abdominal aorta for renal arteriography. Clinically, the use of such techniques is objectionable. Thus clinical application appears to depend upon the development of a roentgenographic tube with an ultra-fine focal spot which will permit currents of 500 ma. or more. Such characteristics were approached by our special tube, which, however, at the maximum milliamperage permitted, possessed a filament life of only about 10 hours. The problem of heat dissipation from the anode under such conditions is a very difficult one to solve, whether one depends upon refinements in the construction of conventional thermal emission roentgen tubes,[1] or hopes for revolutionary developments in the newer field emission roentgen tubes.[2] At any rate, further important advances in the increased visualization of the finer ramifications of the vascular tree will depend in part upon the achievement of electron current densities much greater than those presently available. This approach is being explored at the present time. Whether the additional information obtained as a result of these efforts will be of significance clinically is still conjectural and will also be the subject of further study.

SUMMARY

The possibility of applying direct roentgenographic magnification to clinical angiography has been explored. A specially constructed roentgen tube with an ultra-fine focal spot (0.3 mm.) having a maximum rating of 250 ma. was used, as well as the ultra-fine focal spot of a conventional double-focus roentgen tube. The conventional target-object and object-film distance relationships were altered to give direct magnification to twice normal size.

Magnified angiograms of renal, cerebral, abdominal, pulmonary, and peripheral vessels were obtained.

The technique proved useful so far only in the peripheral and pulmonary vessels where the low permissible milliamperage was not a serious disadvantage because penetration was not a problem. For magnification of such core structures in the adult human as the heart and kidneys, sources of roentgen rays will have to be modified to provide electron current densities much greater than those presently available.

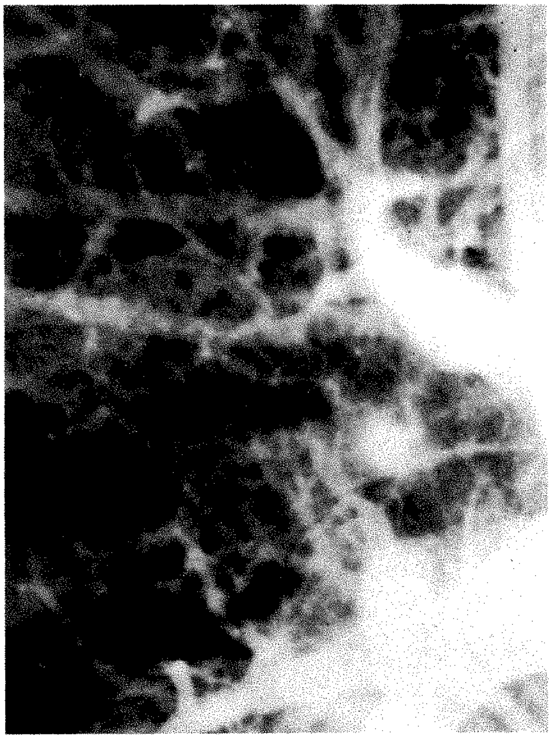

Fig. 4. Pulmonary angiogram using direct roentgenographic magnification to demonstrate the fine vasculature of the lung.

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We wish to acknowledge the invaluable assistance of Edgar L. Greene, Clarence D. Boone, Frank F. Tolley, and William A. Williams in the development of these techniques.

ADDENDUM

Since the preparation of this report, digital and selective renal arteriograms, as well as lymphangiograms have been obtained in 15 additional patients by essentially the same techniques, with good results.

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THE ROENTGEN CONTRAST MEDIA POTENTIATION OF NEMBUTAL ANESTHESIA IN RATS*

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IN THE course of a previous investigation of the protein binding properties of roentgen contrast media, an incidental observation was made that appeared to relate depth of anesthesia in rats to the concomitant injection of certain contrast materials. Since this observation, if substantiated, might prove to be of both theoretic and practical significance, the following experiments were undertaken.

METHODS

1. Stock white female Wistar rats of average adult weight (approximately 250 gm.) were anesthetized with 36 mg. per kg. of nembutal* given intraperitoneally. Immediately after the induction of anesthesia, the animals were injected intramuscularly with 70 per cent urokon† at a dosage schedule of 4,900 mg. per kg. The period of time elapsing from the onset of anesthesia to the first spontaneous indication of wakefulness was noted and recorded.

2. Similarly anesthetized groups of rats were injected with 15 per cent rheomacrodax,‡ a low molecular weight dextran preparation (10.0 cc. per kg. intraperitoneally).

3. Another group of anesthetized rats was injected with intramuscular urokon and rheomacrodax in the dosages noted.

4. Control groups for anesthesia duration consisted of rats injected with nembutal alone, with nembutal and normal saline, and with nembutal and rheomacrodax in the dosages indicated. Since rheomacrodax was supplied in a 5 per cent dextrose solution in water, a further control group was run with urokon and nembutal as noted, in addition to 5 per cent dextrose in water (10 cc. per kg. intraperitoneally).

5. In another set of experiments, the potentiation of nembutal narcosis by graduated dosages of urokon in rats injected with a standard rheomacrodax dosage was determined.

6. To evaluate the duration of survival after injection of a lethal dose of urokon, 16,100 mg. per kg. of 70 per cent urokon was injected intraperitoneally (approximately 3 times the LD_{50} intravenous dosage), in groups of rats (a) without other drugs, (b) with 10 cc. per kg. of 15 per cent rheomacrodax, (c) with 36 mg. per kg. of 6 per cent nembutal, and (d) with 36 mg. per kg. of 6 per cent nembutal and 10 cc. per kg. of 15 per cent rheomacrodax.

7. Groups of rats were subjected to controlled atmospheres of ether, and total sleep time was determined after subsequent injections of 70 per cent urokon (4,900 mg. per kg. of 70 per cent solution intramuscularly). These were matched against control rats injected with normal saline and subjected to the same ether atmosphere.

8. Total sleep time was determined in a group of rats in which an equivalent amount of 50 per cent hypaque* was substituted for 70 per cent urokon. Similar determinations were made in rats with injections of 52 per cent cholografin† in place of urokon.

9. Rabbits were substituted for rats in the urokon-sleep potentiation studies.

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[*] Sodium pentobarbital—Abbott.
[†] Sodium acetrizoate—Mallinckrodt Chemical Works.
[‡] Pharmacia Laboratories.

[*] Sodium diatrizoate—Winthrop Laboratories.
[†] Sodium and methylglucamine iodipamate—Squibb.

[*] Supported by N.I.H. Grant A-5414.
From the Department of Radiology, University of Pittsburgh School of Medicine and the Presbyterian-University Hospital, Pittsburgh, Pennsylvania.
Presented in part at the Tenth International Congress of Radiology, Montreal, Quebec, Canada, September 1, 1962.

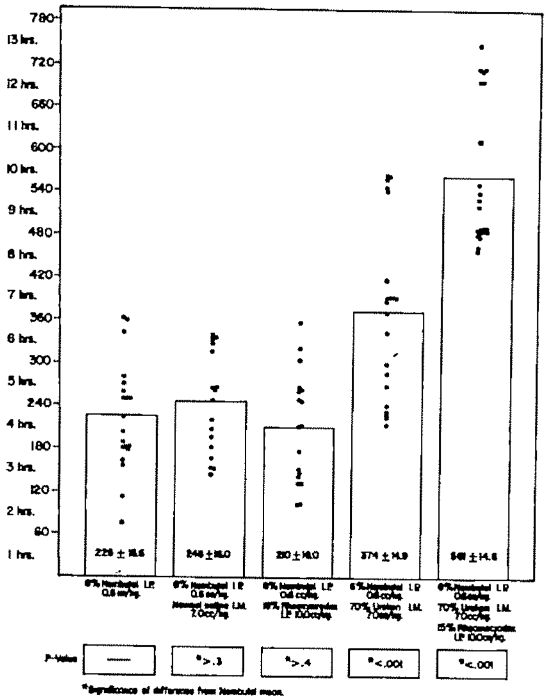

FIG. 1. Prolongation of nembutal narcosis by urokon and urokon-rheomacrodax.

10. In a number of these procedures, the amount of I^{131} labeled urokon that could be recovered from the brains of animals with urokon potentiation of nembutal anesthesia was determined. Similarly, trypan blue, injected intraperitoneally prior to narcotization, was utilized as an indicator of blood-brain barrier integrity in sample animals.

RESULTS

With a constant nembutal dosage of 36 mg. per kg. intraperitoneally, the average duration of narcosis was 226 ± 15.6 minutes. This was not altered significantly by the addition of 15 per cent rheomacrodax intraperitoneally or normal saline intramuscularly. When the animals were injected concomitantly with 70 per cent urokon, the average period of narcosis increased to 374 ± 14.9 minutes. When a group of animals was injected with both nembutal and urokon as noted but received in addition rheomacrodax intraperitoneally, the nembutal narcosis was further potentiated to a mean level of 561 ± 14.6 minutes. The statistical significance of these findings and the distribution values can best be noted by reference to Figure 1.

When the nembutal dosage and the rheomacrodax dosage were maintained and increasing amounts of urokon were injected, there appeared to be a step-wise increase in the potentiation of the nembutal narcosis. This is shown in Figure 2.

Since nembutal-anesthetized rats injected with rheomacrodax and urokon slept longer on the average than similar rats injected with urokon alone, it was thought advisable to determine whether the additional potentiating effect of rheomacrodax might be due in part to the 5 per cent dextrose-water in which the rheomacrodax was prepared. Rats receiving an equivalent amount of dextrose in water, however, failed to show any further potentiation of nembutal-urokon narcosis (average sleep time 381 ± 14.9 minutes). It was apparent, then, that the dextrose solution did not of itself contribute to the potentiation of nar-

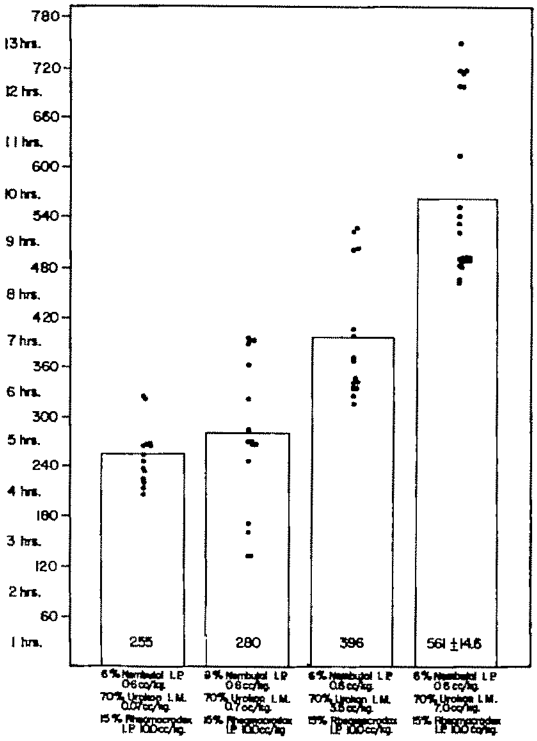

FIG. 2. Effect of graduated urokon dosages on urokon-rheomacrodax narcosis potentiation.

cosis in the rats injected with rheomacrodax, urokon and nembutal.

When the urokon dosage was increased to a level approximately twice that of the established LD_{50} intravenous dose and injected intraperitoneally, with and without nembutal anesthesia, and with and without concomitant rheomacrodax injections, almost all rats expired within several hours. A statistically significant increase in mean survival times, however, resulted in the group of rats given nembutal anesthesia with the urokon and more so when rheomacrodax was also added. It is noteworthy that rheomacrodax without nembutal produced no significant increase in mean survival time in these nonanesthetized rats (Fig. 3).

When 50 per cent hypaque was substituted for urokon in equivalent dosages, potentiation of nembutal narcosis did not occur (Fig. 4). Cholografin, on the other hand, produced considerable potentiation of nembutal anesthesia, even at dosages amounting to half the molar equivalence of urokon (see details in ensuing discussion).

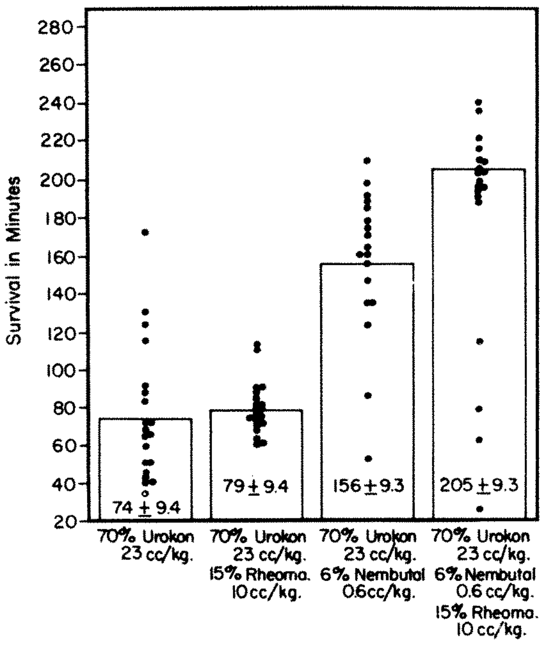

Fig. 3. Duration of survival after injection of lethal dose urokon.

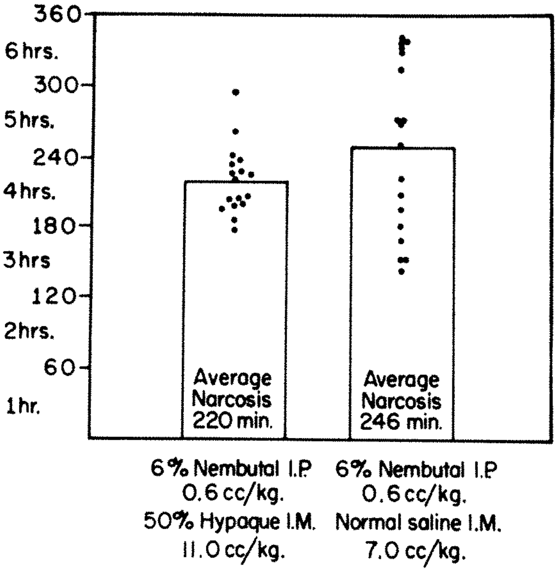

Fig. 4. Effect on nembutal narcosis of hypaque.

Ether anesthesia in rats could not be potentiated by concomitant urokon injections. Groups of rats injected with urokon in dosages similar to those of the nembutal experiments awakened at approximately the same time as did their controls injected with normal saline in a controlled ether chamber. Likewise, the substitution of rabbits for rats in the urokon-nembutal experiments led to a failure of sleep potentiation.

In a number of experiments an attempt was made to determine the average amount of I^{131} labeled urokon that accumulated in the total brain when sleep potentiation was produced with this substance at dosages of 4,900 mg. per kg. At no time could more than 0.5 per cent of the total injected dose of urokon be recovered in whole brain counts averaged out for groups of rats sacrificed at varying intervals after injection. In these animals, no attempt was made to wash out the blood in the cerebral circulation. Similarly in a number of animals, 5 cc. of 0.1 per cent solution of trypan blue injected into the peritoneal cavity failed to discolor the brain in rats injected with nembutal and urokon in the dosages mentioned and sacrificed at varying intervals over a 24 hour period.

COMMENT

The results of these series of experiments indicate that rats under nembutal anesthesia, injected concomitantly with varying amounts of urokon, or urokon together with low molecular weight dextran, show potentiation of the expected nembutal narcosis without alteration of the so-called "blood-brain barrier." There is, furthermore, evidence from these studies that the noted potentiation of nembutal narcosis is reflected in an increase in the immediate survival time of rats injected with very high dosages of urokon.

On reviewing the literature, we encountered the following quotation in a paper of McAfee and Willson[13] in 1956: "It is the impression of the anesthesia department of the Johns Hopkins Hospital that the duration and depth of depression after aortography under Pentothal are greater than is usually seen in surgical patients receiving a similar amount of Pentothal." They were unable to determine a rationale for this observation but suggested the possibility that the pentothal depression might be increased synergistically by the contrast media. These authors do not specify a particular contrast material, but it is evident from case reports cited in the same article that 70 per cent urokon was being used in their aortographies at that time. It was interesting to find also that Killen, Lance, and Owens,[7] while working with dogs in an experimental evaluation of the toxicity of certain contrast media in aortography, noted incidentally what appeared to be a potentiation of the barbiturate (nembutal) anesthesia by urokon.

A number of compounds are known to potentiate barbiturate anesthesia *in vivo.* This list includes the nitro and halophenols, inorganic nitrates, nitrites and iodides, certain organic iodine compounds, glucose and its metabolic products, antihistamines, adrenalin, serotonin and many others.[2,4,8,9,16,17,19] The mechanism of this potentiation has not yet been identified. Additive brain depression, increased permeability of the brain capillaries, concentration alterations in the plasma and tissue fluids resulting from injections of substances with a high osmotic pressure into the peritoneal cavity, alteration of the brain threshold to the barbiturate and many other theories have been proposed. None of these, however, appear to be consistently applicable.

Existing evidence suggests that the depression of cellular activity in the brain that results from barbiturate administration is fundamentally a result of depression of high energy phosphate bond formation without significant reduction of oxygen consumption.[3] This selective depression of phosphorylation without significant alteration in oxidation in the course of energy utilization has been termed "uncoupling" and can be quantitated *in vitro* by the utilization of properly prepared mitochondrial preparations. Selective depression of phosphate bond formation in this fashion is a property shared by many nonanesthetic drugs. While barbiturates do not show a selective preferential affinity for brain,[16] it is evident that their concentration in this organ must exceed that of other equally effective uncoupling agents that do not produce narcosis if the uncoupling predication is to be valid.

In a general way, it seems evident that the prolongation of barbiturate narcosis beyond a control value by a second drug could result from either slowing of the metabolic degradation or excretion of the barbiturate, or from decreasing the brain threshold to the barbiturate. It might also result, however, from increasing the permeability of the blood-brain barrier or decreasing the total metabolic rate and temperature of the animal.[16]

Of the possible mechanisms just enumerated, the present observations are best explained by what appears to be an alteration in the metabolic degradation and excretion of sodium pentobarbital predicated on the basis of comparative protein binding dynamics. To support this hypothesis, one might consider the following facts:

1. Both the contrast material and nembutal are partially bound to albumin in the plasma and in the tissue spaces, and presumably in some intracellular locations as well. The binding of the contrast media has been detailed in a previous communication.[11] The avidity of the bond to albumin varies from one contrast material to another and from species to species. Nembutal has been shown to be predominantly bound to albumin in rats at the injection levels utilized in our studies.[12,15,16]

2. At the relative concentrations pertaining *in vivo* in our study, however, sodium pentobarbital could only minimally displace I^{131} labeled urokon from albumin binding sites in competitive equilibrium dialysis.[10] Presumably, then, at the relative concentrations employed, sodium pentobarbital could not compete favorably with urokon for these binding sites. In this circumstance, the total amount of bound nembutal would be diminished in favor of an increase in the unbound, freely diffusable fraction in the circulating plasma and in the tissue spaces.

3. We found neither significant penetration of I^{131} labeled urokon into the central nervous system nor evidence of alteration of permeability of the blood-brain barrier with potentiation of nembutal narcosis.

In the light of these facts, one might hypothesize that urokon potentiates anesthesia in our experimental circumstances by occupying binding sites on albumin to the relative exclusion of nembutal from these areas. This in turn promotes a higher concentration of unbound diffusable nembutal free to penetrate the central nervous system. It also imposes on nembutal a limitation on albumin transport mechanisms to liver conjugation sites and renal excretory sites, and infers a relative exclusion from the hepatic parenchymal cell with its preference for the more avid binders. Since a dynamic equilibrium pertains, it is expected that the percentage of bound nembutal will increase in relation to the unloading of the bound contrast material by the animal's excretory mechanisms. Reference to Figure 2 will emphasize the almost linear relation between increasing dosages of urokon and increasing narcosis potentiation in the animals injected with combinations of nembutal, urokon and rheomacrodax.

The additive potentiation of anesthesia noted in the rheomacrodax-urokon-nembutal animals was at first difficult to explain. Rheomacrodax is essentially a polymer of glucose and the potentiation of barbiturate anesthesia by glucose and its metabolic products is as yet unexplained.[9] These products are not uncoupling agents and rheomacrodax by itself did not increase the average nembutal narcosis. Recent electrophoretic evidence cited by Ponder and Ponder[14] indicates that dextran coats, or more generally speaking, interacts with serum albumin and it was at first thought possible that this might bear on the additive nembutal potentiation. Previous *in vitro* experiments in this laboratory, however, had failed to indicate any interference by low molecular weight dextran in the binding of I^{131} urokon to albumin. It then occurred to us that perhaps dextran interfered with the excretion of urokon in the rat and this in turn accounted for the nembutal potentiation. The linear relationship between nembutal potentiation and urokon dosage in the group of rats under consideration supported this possibility. Accordingly, 10 rats injected with I^{131} labeled urokon and nembutal were compared with 10 rats injected with I^{131} labeled urokon, nembutal and rheomacrodax for total urinary excretion at 2 hour postinjection sacrifice. All rats underwent urethral ligation at the beginning of the experiment. The bladder contents aspirated at the time of the 2 hour sacrifice showed an average of 15 per cent of the injected urokon in the animals without rheomacrodax and an average excretion of 7.8 per cent in the animals that had received rheomacrodax along with urokon and nembutal. Only 2 per cent of the injected urokon could be recovered in the intraperitoneal fluid aspirates of the animals injected with rheomacrodax. Counts made of the animal carcasses after aspiration of the urinary bladder contents in both groups of animals in comparison with a standard of the injected material counted under similar geometric circumstances was also done. Total counts of the bladder aspirates and the residual rat carcasses in each group showed approximately an 80 per cent accountability of the total injected urokon.

It is evident, then, that the additive potentiation of low molecular weight dextran in these rats could be in large part due to a retarded excretion of urokon. This excretory diminution could not be ascribed in significant degree to osmotic trapping of urokon in the peritoneal cavity and cannot at this time be satisfactorily explained. Of interest in this regard, however, may be the observation by Theile and Theile[18] in children that the intravenous injection of polyvinylpyrollidone (PVP) and dextran led not only to dilution caused by the infused fluid but led also to an increase in protein in the interstitial tissues derived from albumin driven out of the bloodstream and into these areas.

To help substantiate the hypothesis of altered binding dynamics as an explanation for potentiation of nembutal anesthesia, three predications have been tested and fulfilled. The first was that contrast media capable of displacing urokon from albumin should potentiate nembutal anesthesia to a greater extent than did urokon. This was verified by substituting cholografin for urokon. Previous studies from this laboratory[11] had indicated a considerable advantage for cholografin in competitive albumin binding in the rat at approximately the same molecular concentrations. When an equivalent concentration of cholografin was substituted for urokon in 20 rats under nembutal anesthesia, all 20 rats died within 48 hours. Of significance, however, was the fact that no rat awakened from anesthesia during this period with almost half the rats continuing under narcosis for 24 hours or longer. The cholografin dosage was then reduced to $\frac{1}{2}$ the molar equivalent of urokon and in these 20 rats, the average sleep time was 340 minutes, almost equal to that noted with twice the quantity of urokon.

The second predication was that contrast media with relatively poor binding potential[11] would not, in equal quantities, enhance nembutal narcosis. This proved to be the case on injection of hypaque (Fig. 4).

The third predication was that utilization of rabbits rather than rats would not produce significant urokon-nembutal narcosis potentiation. Previous competitive binding studies had indicated that for an equal molar concentration of urokon (1.03×10^{-7} M) rats showed approximately a four fold advantage over rabbits in bound to unbound urokon ratios.[11] Accordingly, rabbits under nembutal anesthesia were injected with intramuscular 70 per cent urokon at a dosage rate of 3,500 mg. per kg. No significant difference could be detected in the total sleep periods for 5 rabbits injected with nembutal and urokon in comparison to 5 rabbits injected with nembutal alone.

All of the evidence cited above seems to lend support to the hypothesis that potentiation of anesthesia by urokon in our test animals is connected with their relative protein binding dynamics. A study of the *in vitro* uncoupling properties of urokon-nembutal combinations in comparison with nembutal alone is now in progress in our laboratories, but it seems unlikely that the potentiation is basically related to the uncoupling mechanism since no enhancement of narcosis resulted with injection of urokon in the ether narcotized animals and ether is an uncoupling agent[6] that, as far as we can determine, has not been shown to interfere with protein binding. It will be of interest to determine the actual nembutal levels in rat brains under the circumstances of our experiment at varying times. This is presently under study, and will be reported in a separate communication.

Finally, consideration should be given to the significance, if any, in experimental toxicity studies, of the roentgen contrast media potentiation of nembutal narcosis. Studies of the toxicity of contrast media and other drugs are often carried out in small animals under barbiturate anesthesia. If, in a comparative study of the toxicity of two related drugs, one is found to potentiate nembutal anesthesia and the other not to, it is obvious that this must be given credence in evaluating specific parameters affected by drug injection in nembutal-narcotized animals.

Hoppe and Archer[5] have shown in experimental animals that the intracisternal toxicity of contrast media was reduced under nembutal anesthesia. Although anesthesia here was associated with reduction in toxicity, it did not abolish the terminal convulsive phenomena, but simply shifted the dose mortality curve to a higher dose level. Furthermore in 1950, Ziperman, Hughes and Shumacker[20] showed that unanesthetized mice given 6,000 mg. of diodrast per kg. of body weight suffered approximately 20 times the immediate (less than 2 hours) mortality of nembutal anesthetized mice. When supplementary injections of nembutal were given subcutaneously 2 hours after the original injection of diodrast and nembutal, 5 out of 5 mice survived. Barbital and seconal also caused a decrease in the immediate mortality with diodrast in this dosage, but only barbital and nembutal in repeated doses caused a statistically significant decrease in total mortality. Neither ether nor procaine caused any change in immediate or total mortality. In our experiments utilizing massive urokon intraperitoneal dosages, a striking parallel between potentiation of narcosis and immediate survival time was demonstrated.

In view of this evidence that appears to correlate sustained barbiturate narcosis with apparent protection of the central nervous system against otherwise toxic dosages of contrast media, one wonders what role should be assigned to the utilization of low molecular weight dextran as noted in recent dog experiments.[1] The role of low molecular weight dextran in enhancing the potentiation of contrast material-nembutal narcosis has been adequately documented in our rats. The applicability of these principles to other animals and other contrast media must await additional experimentation. These concepts are under scrutiny in our laboratory and will be further elucidated in subsequent reports.

CONCLUSIONS

1. The duration of nembutal anesthesia in rats injected with varying quantities of urokon exceeded that of control rats injected with normal saline.

2. Further enhancement of this anesthesia potentiation resulted from injections of low molecular weight dextran and urokon. Dextran itself had no effect, and in combination with urokon, appeared to function by a retardation of the rate of urokon excretion.

3. Hypaque, substituted for urokon, did not prolong nembutal narcosis. Cholografin prolonged narcosis considerably beyond that noted with urokon.

4. When ether was substituted for nembutal, no anesthetic potentiation resulted from urokon injections. When rabbits were substituted for rats, no potentiation could be produced.

5. All of the above findings may be explicable on a postulated system of competitive binding to plasma and tissue albumin sites, and would be entirely compatible with relative binding dynamics noted in a previous communication.[11] A similar mechanism may be operative in some other reported instances of barbiturate potentiation by a host of substances.

6. Nembutal anesthesia appears to confer some degree of protection on rats in the period immediately after injection of a lethal dose of urokon. This period of protection appears to be extended by measures that have been shown to extend the duration of nembutal narcosis.

7. In view of these findings and of perti-

nent previous observations by others cited in the body of this report, extra caution is urged in the interpretation of central nervous system data obtained by experimental procedures on small animals under barbiturate anesthesia.

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Forty-sixth Annual Meeting: Greenbrier Hotel, White Sulphur Springs, W. Va., April 13–16, 1964.

EDITORIAL

THE ROLE OF THE RADIOLOGIST IN CARDIAC DIAGNOSIS IN THE COMMUNITY HOSPITAL

THERE is a continuing need in community hospitals for the establishment of cardiovascular diagnostic units emphasizing angiocardiography. The type of unit must necessarily depend upon the size of the community and the availability of trained professional personnel. There are two components of the cardiovascular system to be considered, the visceral-peripheral vascular and the cardiac. Although related, the problems involved in providing a service in each sphere differ.

The extracardiac vascular segment can and should be performed in every hospital almost regardless of size. The need for this service has been well demonstrated. The cost of the necessary equipment is moderate.

In contrast, the establishment of a complete cardiac diagnostic unit is costly and it is, therefore, probably, wise for the professional and lay leaders of the community to select one particular hospital to serve the diagnostic needs of the entire community until the volume of work warrants the establishment of an additional unit. Frequently, due to noncoordinated planning, there exists some type of cardiac diagnostic unit in several hospitals within one community of moderate size. This is regrettable: the volume of case material is diluted and the opportunity to develop a complete and expert service is not realized.

Ideally, the efforts of a cardiologist, cardiac physiologist and radiologist should be combined to achieve the best results, with the radiologist assuming the entire responsibility for the performance and interpretation of the angiocardiographic portion of the procedure. The degree of active participation by the radiologist varies in different institutions; not infrequently, it is too minor a role. A combination of factors has produced this situation: a lack of experience in a relatively new field of endeavor, a hesitancy among some radiologists to accept the responsibility of potential complications inherent in technical procedures and economic factors with established radiologists finding no need to gain proficiency in a new field. Obviously, the various radiologic training centers throughout the country are partially responsible for the inertia. Several centers are now offering fellowships in Cardiovascular Radiology following completion of residency training in Radiology. An adequate knowledge and proficiency in this type of work can be acquired during a 6 to 12 month training period. The importance of this aspect of radiologic training is emphasized by The American Board of Radiology which now requires a basic knowledge of this field by the candidate.

The ideal situation, a complete unit and staff, is not always possible in the urban community since not only are there too few cardiovascularly oriented radiologists, but, also too few cardiac physiologists. While it is true that there are patients with conditions requiring the efforts of all the members of the cardiac diagnostic unit, it is also true that there are other patients who require only the services of a trained radiologist. I refer, in particular, to the use of forward angiocardiography which, I believe, is the best initial procedure in diagnosing cyanotic heart disease in infants. There are two considerations which dictate this diagnostic approach. First, the majority of infants with cyanotic heart disease usually show a combination of defects with complex patterns of intracardiac flow which makes catheterization data difficult to interpret. Second, it is usually not necessary to define in detail the anatomic and physiologic abnormalities but merely to display the major aspects of the malformation and thus separate the potentially correctable from the noncorrectable case. The information obtained from forward angiocardiography will often solve the diagnostic problem and preclude an expensive and anxious trip for patient and relatives to some distant medical center. For some young families with limited income, the expense involved in making such a trip can be financially exhausting.

If any radiologist with cardiovascular experience is interested in developing a cardiac diagnostic unit in his community, this is one area in which he might begin. A satisfying service is achieved, the examination is relatively easy to perform, the risk is minimal and in many cases nothing further need be done diagnostically.

The previous considerations constitute the major aspect of the problem. What about the situation where the patient has a lesion deemed potentially correctable? The next step depends on the availability of a trained cardiac surgeon in the community. If the surgeon is available, then the radiologist should be ready to assume the responsibility of the additional procedures which are warranted unless all features of the malformation are obvious on the forward angiocardiogram. Too often infants have been operated on with incomplete anatomic definition of the anomaly. Here again, the most revealing diagnostic studies are those utilizing contrast material—selective angiocardiography and/or selective aortography; the chamber or vessel selectively visualized is often dependent on the findings of the preceding forward angiocardiogram. While it is true that the potential complications in selective procedures are greater than in forward angiocardiography, a carefully performed study carries a minimal risk. Certain equipment and drugs should be nearby in case of an emergency and a close working relationship with the anesthesia department is always desirable.

In conclusion, the pattern of responsibility for special procedures in cardiac diagnosis is fairly well established in University centers. What happens now and in the future in urban communities will depend, in large part, on those radiologists who recognize the cardiovascular needs of the community and are willing to accept the responsibility of establishing the service and performing the procedures. For years, the need for the radiologist to assume a physician's mantle has been emphasized in the radiologic literature. Words will not significantly change the situation, but concentrated effort and a willingness by the radiologist to accept responsibility for special procedures will.

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NEWS ITEMS

NEW OFFICERS OF THE AMERICAN CLUB OF THERAPEUTIC RADIOLOGISTS

At the last meeting of the American Club of Therapeutic Radiologists, held in Chicago on November 18, the following new officers were elected: *President:* Dr. Franz J. Buschke, San Francisco, California; and *Vice-President:* Dr. Milford D. Schulz, Boston, Massachusetts. Dr. Howard B. Latourette, *Treasurer*, and Dr. J. A. del Regato, *Secretary*, were reelected.

The office of the Secretary is at the Penrose Cancer Hospital, Colorado Springs, Colorado.

SPRING CONFERENCE OF THE NEW YORK ROENTGEN SOCIETY

Announcement is made of the Spring Conference of the New York Roentgen Society which will be held at the Waldorf-Astoria in New York City, April 23, 24 and 25, 1964. A special scientific program has been arranged. The meeting will coincide with the opening of the New York World's Fair.

For further information please contact Francis F. Ruzicka, Jr., M.D., Secretary, St. Vincent's Hospital, New York 11, New York.

POSTGRADUATE COURSE IN RADIOLOGY AND RADIOACTIVE ISOTOPES

The annual three day postgraduate course in Radiology and Radioactive Isotopes will be presented February 17, 18 and 19, 1964, at the University of Kansas Medical Center.

An outstanding guest faculty, selected for their teaching as well as clinical abilities, has been assembled for this program. Recent advances in some of the newer developments of radiology will be discussed along with a review of some of the basic problems confronting the radiologist and the internist.

For further information please write to William D. Nelligan, Executive Director, Department of Postgraduate Medical Education, University of Kansas Medical Center, Rainbow Boulevard at 39th Street, Kansas City 3, Kansas.

SYMPOSIUM ON CELLULAR RADIATION BIOLOGY

The University of Texas M. D. Anderson Hospital and Tumor Institute will present the Eighteenth Annual Symposium on Fundamental Cancer Research, "Cellular Radiation Biology," on March 2, 3 and 4, 1964, in the Emerald Room of the Shamrock Hilton Hotel, Houston, Texas.

Registration: Sunday, March 1, 2:00–9:00 P.M., at the Hotel Convention Desk in the lobby of the Shamrock Hilton Hotel, and Monday, March 2, 8:15–8:45 A.M., in the Grecian Room of the Shamrock Hilton Hotel; thereafter, at the Hotel Convention Desk. Preregistration would be appreciated. It is recommended that hotel reservations be made well in advance of the symposium.

The Registration Fee is $5.00; please make check payable to M. D. Anderson Hospital. The registration fee will be waived for students, including residents and fellows who preregister prior to March 2, 1964.

COURSE IN CLINICAL USE OF RADIOACTIVE ISOTOPES

A course in the Clinical Use of Radioactive Isotopes will be given under the supervision of Dr. Sergei Feitelberg and Dr. Edith Quimby of the Department of Radiology, Columbia University, New York City, from June 1 through June 26, 1964.

This is a full-time course which includes lectures, experimental laboratory exercises, clinical rounds and clinical measurements on patients and on specimens. In addition to Drs. Feitelberg and Quimby, the teaching staff will include a number of invited lecturers from the New York area, each presenting material in his own special field.

Enrollment in the class is limited to 20; the fee is $300.

Inquiries should be addressed to Dr. Sergei Feitelberg, Mt. Sinai Hospital, Fifth Avenue at 100th Street, New York, New York.

THIRTY-SIXTH ANNUAL CONVENTION OF THE AMERICAN SOCIETY OF X-RAY TECHNICIANS

The American Society of X-Ray Technicians will hold its Thirty-sixth Annual Convention at the Leamington Hotel in Minneapolis, Minnesota, May 30–June 5, 1964.

For further information please contact Sister Mercedes, R.T., Chairman, Publicity Committee, St. Joseph's Hospital, 69 West Exchange Street, St. Paul 2, Minnesota.

EIGHTH INTERAMERICAN CONGRESS OF RADIOLOGY

The Executive Committee of the Eighth Interamerican Congress of Radiology has the honor of inviting all the Radiologists, Physicists, and Scientists working in the field of Radiology to attend the Congress which will be held in Caracas, Venezuela, October 2–9, 1964.

The Commissions of Diagnostic Radiology, Radiotherapy and *Nuclear Medicine* are working on the preparation of their respective programs, and have chosen the following topics for the preliminary agenda: (1) the teaching of radiology in America; (2) progress in pediatric radiology; (3) radiologic exploration of the cranial posterior fossae; (4) lymphadenography; (5) progress in radiobiology; (6) radiotherapy and chemotherapy; (7) treatment of the central nervous system tumor; (8) radiation protection and others. Refresher courses will be given in: radiation physics; radiology of the small intestine; selective angiography and angiocardiography; functional studies of the kidney, and others.

The Commissions of Social Affairs and *The Ladies' Committee of the Congress* are preparing an interesting program in collaboration with the Macuto Sheraton Hotel, the Social Centers of the City and Mountain Clubs to provide the participants of the congress and especially their families with a very pleasant vacation, alternating between sea resort sojourns, sight-seeing city tours and mountain excursions. The climate at this time of the year is excellent for full enjoyment of such a program.

The Congress will be held at the new luxurious Macuto Sheraton Hotel, which has the most modern conveniences, including air-conditioned rooms and suites, all with balconies and private bathrooms, 2 swimming pools, a beautiful white sand beach and all kinds of facilities for sailing, motor boating, water skiing, etc. Prices for single rooms are $9.00 to $11.00 per day and for double rooms $12.00 to $16.00 per day (European plan). In front of the Macuto Sheraton Hotel there is the Caraballeda Club with a beautiful Golf Course.

Those interested in more information please write to Dr. Ruben Merenfeld, *Secretary-General*, Apartado 9362 Candelaria, Caracas, Venezuela.

BOOK REVIEW

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

The Spine; A Radiological Text & Atlas. By Bernard S. Epstein, M.D., Chief, Department of Radiology, The Long Island Jewish Hospital, New Hyde Park, New York and Clinical Professor of Radiology, The Albert Einstein College of Medicine, New York. Cloth. Price $16.50. Lea & Febiger, Philadelphia, 1962. Second Edition. Pp. 616, with 393 illustrations.

An acquaintance with the First Edition of this textbook on the vertebral column enabled one to recognize Dr. Epstein as one of the world's leading authorities on the roentgen examination of the spine. The present Second Edition contains numerous illustrations and revisions in line with newer developments.

Chapter 1 evaluates and describes the normal spine. The author has revised or added to the sections on embryology, the spinal ligaments, intraspinal dimensions, diskography and major revisions were made in the section on myelography.

Various revisions in Chapter 2 include sections on anomalies of the occiput, the atlas and axis. The Arnold-Chiari malformation and platybasia are other conditions described.

Chapter 3 deals with diseases of congenital, endocrine and metabolic origin. Additions to the First Edition are sections on osteochondrodystrophy, gargoylism, dysplasia epiphysialis multiplex, metaphyseal dysplasia, hypophosphatasia and idiopathic hypercalcemia in infancy.

Chapter 5 contains descriptions of vertebral column neoplasms and supplemental material on reticulum cell sarcoma, spinal lymphomas, benign chondroblastoma, massive osteolysis and benign osteoblastoma.

Major revision and extensive additions to the subject of spinal traumatic changes are seen in Chapter 6 and in Chapter 7; the section on herniated intervertebral disks likewise is expanded.

The author has condensed a vast amount of material into an excellent working textbook which should be a part of the radiologist's library as those who have read the First Edition are aware. To radiologic residents, orthopedic surgeons and allied specialists interested in the spine, this Second Edition is also highly recommended.

Robert L. Willis, Jr., M.D.

BOOKS RECEIVED

Carcinoma of the Vulva: an Analysis of 560 Patients with Histologically Verified Squamous Cell Carcinoma. Supplement 217. By Folke Edsmyr from Radiumhemmet Karolinska Sjukhuset, Stockholm 60, Sweden. Paper. Pp. 135, with 9 illustrations and 52 tables. Price, Sw.Kr. 30. Acta radiologica, P. O. Box 2052, Stockholm 2, Sweden, 1962.

Wasserlösliche, Viskosierte Wasserlösliche und Jodölige Kontrastmittel in der Hysterosalpingographie: Vergleichende Untersuchungen. Supplement 218. By P. Soila, M. Grönroos, O. Kauppila and L. Pyykönen, aus der Obstetrischen und Gynäkologischen Klinik und der Röntgenklinik des Universitäts-Zentralkrankenhauses Turku, Finnland. Paper. Pp. 75, with 24 illustrations and 7 tables. Price, Sw.Kr. 25. Acta radiologica, P. O. Box 2052, Stockholm 2, Sweden, 1962.

Hiatal Incompetence: Studies on Mechanics and Principles of Examination for Hiatus Hernia and Gastro-oesophageal Reflux. Supplement 219. By Stig Sandmark from the Department of Otolaryngology and the Roentgen-Diagnostic Department, University Hospital, Lund, Sweden. Paper. Pp. 46, with 19 illustrations. Price, Sw.Kr. 25. Acta radiologica, P. O. Box 2052, Stockholm 2, Sweden, 1963.

Free Movements in the Temporomandibular Joint: a Cineradiographic Study. Supplement 220. By Max Lundberg from the Department of Roentgenology and the Department of Prosthetics, The Royal School of Dentistry, Stockholm, Sweden. Paper. Pp. 77, with 32 illustrations and 25 tables. Price, Sw.Kr. 30. Acta radiologica, P. O. Box 2052, Stockholm 2, Sweden, 1963.

Selective Angiography of the Hepatic Veins: Experimental Investigations of Basal Circulatory Dynamics. Supplement 221. By Åke Norhagen from the Department of Roentgenology and the Department of Thoracic Medicine, Thoraxklinikerna, Karolinska Sjukhuset, Stockholm, Sweden. Paper. Pp. 121, with 64 illustrations. Price, Sw.Kr. 35. Acta radiologica, P. O. Box 2052, Stockholm 2, Sweden, 1963.

Genetically Significant Radiation Doses in Diagnostic Radiology. Supplement 222. By Erling Hammer-Jacobsen from the Radiological Department, Rigshospitalet and the Radium Centre of Copenhagen, Denmark. Paper. Pp. 277, with 15 illustrations. Price, Sw.Kr. 35. Acta radiologica, P. O. Box 2052, Stockholm 2, Sweden, 1963.

Alkoxyglycerols and Their Use in Radiation Treatment: An Experimental and Clinical Study. Supplement 223. By Astrid Brohult from Radiumhemmet, Karolinska Sjukhuset, Stockholm, 60, Sweden. Paper. Pp. 99, with 13 illustrations. Price, Sw.Kr. 30. Acta radiologica, P. O. Box 2052, Stockholm 2, Sweden, 1963.

Premiers Éléments de Microradiographie Clinique (Crane et Os Longs). By M. Juster, Maître de Recherches au C. N. R. S.: H. Fischgold, Professeur à la Faculté de Médecine de Paris: and M. Laval-Jeantet, Attaché de Recherches au C. N. R. S. Paper. Pp. 186, with 128 illustrations. Price, 60 F. Masson & C^{ie}, Éditeurs, 120 Boulevard Saint-Germain, Paris, 1963.

Quantitative Chemical Techniques of Histo- and Cytochemistry. By David Glick, Ph.D., Head, Division of Histochemistry; Professor, Department of Pathology, Stanford University Medical School, Palo Alto, California. Volume II. Cloth. Pp. 514, with some illustrations. Price, $15.75. John Wiley & Sons, Inc., Publishers, 605 Third Avenue, New York 16, N. Y., 1963.

The EMG: A Guide and Atlas for Practical Electromyography. By Forbes H. Norris, Jr., M.D., Associate Professor of Neurology and Acting Chairman of the Neurology Division, Department of Medicine, University of Rochester, and Senior Associate Physician, Strong Memorial Hospital, Rochester, New York. Cloth. Pp. 135 with 42 illustrations. Price, $4.75. Grune & Stratton, Inc., 381 Park Avenue South, New York 16, N. Y., 1963.

An Atlas of Vascular Rings and Related Malformations of the Aortic Arch System. By James R. Stewart, M.D., M.S. in Radiology, Consultant, Section of Roentgenology, Mayo Clinic, Rochester, Minnesota; Owings W. Kincaid, M.D., M.S. in Radiology, Consultant, Section of Roentgenology, Mayo Clinic, Assistant Professor of Radiology, Mayo Foundation Graduate School, University of Minnesota, Rochester, Minnesota; and Jesse E. Edwards, M.D., Presently, Director of Laboratories, Charles T. Miller Hospital, St. Paul, Minnesota, Clinical Professor of Pathology, School of Medicine, University of Minnesota, Minneapolis, Minnesota. Cloth. Pp. 172, with many illustrations. Price, $10.75. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1963.

The Chest Film in Massive Pulmonary Embolism. By Daniel J. Torrance, Jr., M.D., Member, Scripps Clinic and Research Foundation, Chief, Division of Diagnostic Roentgenology, La Jolla, California; Formerly, Associate Professor, The Johns Hopkins University School of Medicine and Chief, Division of Diagnostic Roentgenology, The Johns Hopkins Hospital and Medical School, Baltimore, Maryland. Cloth. Pp. 74, with 31 illustrations. Price, $6.75. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1963.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: Radisson Hotel, Minneapolis, Minn., Sept. 29–Oct. 2, 1964.

American Radium Society
Secretary, Dr. Justin J. Stein, U.C.L.A. Medical Center, Los Angeles 24, Calif. Annual meeting: Greenbrier Hotel, White Sulphur Springs, W. Va., April 13–16, 1964.

Radiological Society of North America
Secretary-Treasurer, Dr. Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb. Annual meeting: Palmer House, Chicago, Ill., Nov. 29–Dec. 4, 1964.

American College of Radiology
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill. Annual meeting: Ramada Inn, Tucson, Ariz., Feb. 5–8, 1964.

Section on Radiology, American Medical Association
Secretary, Dr. Clyde A. Stevenson, Sacred Heart Hospital, West 101 Eighth Ave., Spokane 4, Wash. Annual meeting: San Francisco, Calif., June 21–25, 1964.

American Board of Radiology
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn. The Spring 1964 examination will be held at the Americana Hotel, New York City, June 8–12, inclusive. Deadline for filing applications was December 31, 1963. There will be a Special Examination in Nuclear Medicine for diplomates in Radiology or Therapeutic Radiology if sufficient applications are received. The Fall 1964 examination will be held at the Americana Hotel, Bal Harbour, Florida, December 7–11, inclusive. Deadline for filing applications is June 30, 1964.

American Association of Physicists in Medicine
Secretary-Treasurer, Charles S. Simons, University of Michigan Hospital, Ann Arbor, Mich. Annual meeting to be announced.

American Club of Therapeutic Radiologists
Secretary, Dr. J. A. del Regato, Penrose Cancer Hospital, Colorado Springs, Colo.

Eleventh International Congress of Radiology
Secretary-General, Professor Dr. Med. Arduino Ratti, via Moscova, 44-1, Milan, Italy. Address inquiries to Professor Dr. Med. Luigi Turano, President-Elect, Istituto di Radiologia, Università di Roma, Rome, Italy. Meeting: September 22–28, 1965.

Eighth Inter-American Congress of Radiology
Counselor for the United States, Dr. Philip J. Hodes, Jefferson Medical College Hospital, 11th and Walnut Streets, Philadelphia 7, Pennsylvania.
Secretary, Dr. Mario Gaitan-Yanguas, Bogotá, Colombia. Meeting to be announced.

Alabama Radiological Society
Secretary, Dr. Walter Brower, Birmingham, Ala. Meets time and place of Alabama State Medical Association.

American Nuclear Society
Treasurer, Raymond Maxson, 86 E. Randolph St., Chicago, Ill. Annual meeting to be announced.

Arizona Radiological Society
Secretary-Treasurer, Dr. E. Lawrence Ganter, 1820 E. Polk St., Phoenix 34, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

Arkansas Radiological Society
Secretary, Dr. Charles W. Anderson, 1108½ Poplar, Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

Association of University Radiologists
Secretary-Treasurer, Dr. Sidney W. Nelson. Annual Meeting: University of Chicago School of Medicine, Chicago, Illinois, May 14–16, 1964.

Atlanta Radiological Society
Secretary, Dr. Donald R. Rooney, Burnt Hickory Road, Marietta, Ga. Meets monthly except during three summer months, on third Tuesday, at the Academy of Medicine, Atlanta, Ga., at 8:00 P.M.

Bavarian-American Radiologic Society
Secretary, Dr. Robert W. Edland, Major MC USA, United States Army Hospital Augsburg, 21st Evacuation Hospital, Chief of Radiology Service, APO 178, New York, N. Y. Meets quarterly.

Blockley Radiological Society
Secretary, Dr. Bernard J. Ostrum, 2412 North 52nd St., Philadelphia, Pa.

Brooklyn Radiological Society
Secretary, Dr. Peter J. Lampros, 121 Dekalb Ave., Brooklyn, N. Y. Meets first Thursday of each month October through May.

Buffalo Radiological Society
Secretary, Dr. Eugene V. Leslie, Edward J. Beyer Memorial Hosp., Buffalo 15, N. Y. Meets second Monday evening each month, October to May inclusive.

California Radiological Society
Secretary, Dr. L. Henry Garland, Suite 1739, 450 Sutter St., San Francisco, Cal. Meets annually during meeting of California Medical Association.

Central New York Radiological Society
Secretary, Dr. Edward W. Carsky, Crouse-Irving Hospital, 820 S. Crouse Ave., Syracuse, N. Y. Meets first Monday each month October through May.

Central Ohio Radiological Society
Secretary-Treasurer, Dr. Harold W. Long, 81 S. Fifth St., Columbus 15, Ohio. Meets third Thursday in October, and second Thursday in November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

Central Society of Nuclear Medicine
Secretary, Dr. Robert S. Landauer, Radiation Center Bldg., 1903 West Harrison St., Chicago 12, Ill.

Chicago Roentgen Society
Secretary, Dr. Abram H. Cannon, 250 E. Superior St., Chicago 11, Ill. Meets second Thursday of each month, October to April except December at the Pick-Congress Hotel at 8:00 P.M.

Cleveland Radiological Society
Secretary-Treasurer, Dr. James Christie, 10515 Carnegie Avenue, Cleveland, Ohio. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and April.

Colorado Radiological Society
Secretary, Dr. David J. Stephenson, 8300 West 38th Ave., Wheat Ridge, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

Connecticut Valley Radiologic Society
Secretary, Dr. James L. Krieger, 85 Jefferson St., Hartford 6, Conn. Meets first Friday in February and April.

Dallas-Fort Worth Radiological Society
Secretary, Dr. Robert D. Moreton, 816 Medical Arts Bldg., Fort Worth, Tex. Meets monthly, third Monday, at Greater Fort Worth International Airport at 6:30 P.M.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

DETROIT ROENTGEN RAY AND RADIUM SOCIETY
Secretary, Dr. Arch H. Hall, Harper Hospital, Detroit 1, Mich. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

EAST BAY ROENTGEN SOCIETY
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland, Calif.

EAST TENNESSEE RADIOLOGICAL SOCIETY
Secretary, Dr. J. Marsh Frere, Jr., 205 Medical Arts Bldg., Knoxville, Tenn. Meets in January and September.

EASTERN CONFERENCE OF RADIOLOGISTS
Secretary, Arrangements Committee, Dr. Theodore A. Tristan, 3400 Spruce St., Philadelphia 4, Pa. Annual meeting to be announced.

EASTERN RADIOLOGICAL SOCIETY
Secretary, Dr. James F. Martin, North Carolina Baptist Hospital, Winston-Salem, N. C.

FLORIDA RADIOLOGICAL SOCIETY
Secretary, Dr. David Kirsh, 712 Du Pont Bldg., Miami, Fla. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

FLORIDA WEST COAST RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Garth R. Drewry, Tampa General Hospital, Tampa 6, Fla. Meets in January, April, July and October.

GEORGIA RADIOLOGICAL SOCIETY
Secretary, Dr. David Robinson, P.O. Box 394, Savannah, Ga. Meets in spring and fall with Annual State Society Meeting.

GREATER MIAMI RADIOLOGICAL SOCIETY
Secretary, Dr. Robert F. Feltman, Dade County Medical Association Building, Two S.E. Thirteenth St., Miami 32, Fla. Meets monthly, third Wednesday at 8:00 P.M. at Jackson Memorial Hospital, Miami, Fla.

GREATER ST. LOUIS SOCIETY OF RADIOLOGISTS
Secretary, Dr. C. M. Witt, #16 Hampton Village Plaza, St. Louis 9, Mo.

HOUSTON RADIOLOGICAL SOCIETY
Secretary, Dr. D. A. Van Velzer, Texas Medical Center Library, Jesse H. Jones Library Bldg., Houston 25, Tex. Meets fourth Monday of each month, except June, July, August and December, at the Doctors' Club, 8:00 P.M., Houston, Tex.

IDAHO STATE RADIOLOGICAL SOCIETY
Secretary, Dr. George H. Harris, Bannock Memorial Hospital, Pocatello, Idaho. Meets in the spring and fall.

ILLINOIS RADIOLOGICAL SOCIETY
Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in the spring and fall.

INDIANA ROENTGEN SOCIETY, INC.
Secretary, Dr. Richard A. Silver, 1815 N. Capitol Avenue, Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

IOWA RADIOLOGICAL SOCIETY
Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

KANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. Roger K. Wallace, Riley County Hospital, Manhattan, Kan. Meets in spring with State Medical Society and in winter on call.

KENTUCKY RADIOLOGICAL SOCIETY
Secretary, Dr. Lawrence A. Davis, 226 East Chestnut St., Louisville, Ky. Meets monthly on second Friday at Sheraton Hotel, Louisville.

KINGS COUNTY RADIOLOGICAL SOCIETY
Secretary, Dr. Stanley Dannenberg, 1917 Bedford Ave., Brooklyn 25, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

KNOXVILLE RADIOLOGICAL SOCIETY
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

LOS ANGELES RADIOLOGICAL SOCIETY
Secretary, Dr. Bernard J. O'Loughlin, Dept. of Radiology, UCLA Center for Health Sciences, Los Angeles 24, Calif. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles.

MAINE RADIOLOGICAL SOCIETY
Secretary, Dr. Charles W. Capron, Maine Medical Center, Portland, Me. Meets in June, September, December and April.

MARYLAND RADIOLOGICAL SOCIETY
Secretary, Dr. Henry Startzman, Medical Arts Building, Baltimore, Maryland.

MEMPHIS ROENTGEN SOCIETY
Secretary-Treasurer, Dr. Irving K. Ettman, 684 W. Brookhaven Circle, Memphis, Tenn. Meets first Monday of each month at John Gaston Hospital.

MIAMI VALLEY RADIOLOGICAL SOCIETY
Secretary, Dr. William D. Roberts, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.

MID-HUDSON RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph Sorrentino, St. Francis Hospital, Poughkeepsie, N. Y. Meets 8:30 P.M., fourth Wednesday of each month September to May.

MILWAUKEE ROENTGEN RAY SOCIETY
Secretary-Treasurer, Dr. Harold F. Ibach, 2400 W. Villard Avenue, Milwaukee 9, Wis. Meets monthly on fourth Monday, October through May, at University Club.

MINNESOTA RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Frank J. Anderson, 810 E. 27th St., Minneapolis 7, Minn. Meets three times annually, in fall, winter and spring.

MISSISSIPPI RADIOLOGICAL SOCIETY
Secretary, Dr. Jack K. Goodrich, University Medical Center, Jackson, Miss. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 P.M.

MONTANA RADIOLOGICAL SOCIETY
Secretary, Dr. John M. Fritts, 1224 S. Higgins Ave., Missoula, Montana. Meets at least once a year.

NASSAU RADIOLOGICAL SOCIETY
Secretary, Dr. Barry L. Lewis, 165 N. Village Ave., Rockville Centre, New York, N. Y. Meets second Tuesday of the month in February, April, June, October and December.

NEBRASKA STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Richard Bunting, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Neb. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

NEVADA RADIOLOGICAL SOCIETY
Secretary, Dr. William G. Arbonies, Department of Radiology, St. Mary's Hospital, Reno, Nev.

NEW ENGLAND ROENTGEN RAY SOCIETY
Secretary, Dr. Robert E. Wise, 605 Commonwealth Ave., Boston 15, Mass. Meets third Friday of each month, October through April, at The Longwood Towers, 20 Chapel Street, Brookline, Mass. at 4:30 P.M.

NEW HAMPSHIRE ROENTGEN RAY SOCIETY
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

NEW MEXICO ASSOCIATION OF RADIOLOGISTS.
Secretary-Treasurer, Dr. Justin J. Wolfson, Department of Radiology, Bernalillo County-Indian Hospital, Albuquerque, New Mexico.

NEW YORK ROENTGEN SOCIETY
Secretary, Dr. Francis F. Ruzicka, Jr., St. Vincent's Hospital, New York, 11, N. Y. Meets monthly on third Monday at the New York Academy of Medicine at 4:30 P.M.

Spring Conference: Waldorf-Astoria Hotel, New York, N. Y., April 23–25, 1964.

North Carolina Radiological Society
Secretary, Dr. Simmons J. Patrick, Lenoir Memorial Hospital, Kinston, N. C. Meets in the spring and fall each year.

North Dakota Radiological Society
Secretary, Dr. John Jestadt, Depuy-Sorkness Clinic, Jamestown, N. D. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Anthony J. Tabacco, 621 Central Ave., Albany 6, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

Northern California Radiological Society
Secretary, Dr. Rob H. Kirkpatrick, 1219 28th St., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

Northwestern Ohio Radiological Society
Secretary, Dr. Anthony F. Lalli, 421 Michigan St., Toledo, Ohio.

Ohio State Radiological Society
Secretary, Dr. M. M. Thompson, Jr., 316 Michigan St., Toledo 2, Ohio. Annual meeting: Cleveland, Ohio, May 23–24, 1964.

Oklahoma State Radiological Society
Secretary, Dr. Simon Pollack, Utica Square Medical Center, Tulsa, Okla. Meets in January, May and October.

Orange County Radiological Society
Secretary-Treasurer, Dr. E. Nicholas Sargent, Orange County General Hospital, Orange, Calif. Meets fourth Tuesday of month except June, July, August and December in Orange County Medical Association Building.

Oregon Radiological Society
Secretary-Treasurer, Dr. James A. Schneider, St. Vincent Hospital, Portland 10, Ore. Meets on second Wednesday of month at 7:00 P.M. at the University Club, Portland, Ore.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. Charles E. Donley, 543 East 4th Street, Bend, Ore. Annual meeting on the second weekend in May, 1964.

Pennsylvania Radiological Society
Secretary-Treasurer, Dr. Frederick R. Gilmore, Clearfield Hospital, Clearfield, Pa. Annual meeting: Buckhill Falls, May 21–23, 1964.

Philadelphia Roentgen Ray Society
Secretary, Dr. Antolin Raventos, Hospital of the University of Pennsylvania, Philadelphia 4, Pa. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Marvin Brodie, 3459 Fifth Ave., Pittsburgh 13, Pa. Meets second Wednesday of month, October through June at Park Schenely Restaurant.

Radiological Society of Connecticut
Secretary-Treasurer, Dr. Orlando F. Gabriele, 1450 Chapel St., New Haven 11, Conn. Meetings are held bimonthly.

Radiological Society of Greater Cincinnati
Secretary, Dr. John F. Popken, Jr., 831 Carew Tower, Cincinnati, Ohio. Meets first Monday of each month at Cincinnati Academy of Medicine.

Radiological Society of Hawaii
Secretary, Dr. Edgar S. Childs, Kuakini Hospital, Honolulu, Hawaii. Meets third Monday of each month at 7:30 P.M.

Radiological Society of Greater Kansas City
Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. Andrew F. Giesen, Ochsner Clinic, New Orleans 15, La. Meets annually during Louisiana State Medical Society meeting.

Radiological Society of New Jersey
Secretary, Dr. E. Arthur Kratzman, 912 Prospect Ave., Plainfield, N. J. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

Radiological Society of the State of New York
Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester 18, N. Y. Annual meeting to be announced.

Radiological Society of South Dakota
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

Radiological Society of Southern California
Secretary-Treasurer, Dr. Charles G. Campbell, La Jolla, Calif.

Redwood Empire Radiological Society
Secretary, Dr. Lee F. Titus, 164 W. Napa St., Sonoma Calif. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, August, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Gerald R. Holzwasser, Rochester General Hospital, Northside Division, 1425 Portland Ave., Rochester 21, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. John H. Freed, 4200 East Ninth Ave., Denver 20, Colo. Annual meeting to be announced.

San Antonio-Military Radiological Society
Secretary, Dr. Hugho F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Tex. Meets third Wednesday each month in Fort Sam Houston Officer's Club at 6:30 P.M.

San Diego Radiological Society
Secretary, Dr. Charles G. Campbell, 6673 Avenida Manana, La Jolla, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary, Dr. Malcolm Jones, University of California Hospital, San Francisco 22, Calif. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco 18, Calif.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Medical Society of the District of Columbia
Secretary-Treasurer, Dr. Martin A. Thomas, 1150 Connecticut Ave., Washington 6, D. C. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Southern Medical Association
Secretary, Dr. John D. Reeves, Department of Radiology, Univ. of Florida College of Medicine, Gainesville, Fla. Annual Meeting to be announced.

Section on Radiology, Texas Medical Association
Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Medical Association.

Shreveport Radiological Club
Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 p.m., September to May inclusive.

Society for Pediatric Radiology
Secretary, Dr. John L. Gwinn, Children's Hospital, Los Angeles 27 Calif. Annual meeting: Radisson Hotel, Minneapolis, Minn., Sept. 28, 1964.

Society of Nuclear Medicine
Secretary, Mr. C. Craig Harris, Oak Ridge National Laboratories, Oak Ridge, Tenn. *Administrator*, Mr. Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting: Claremont Hotel, Berkeley, Calif., June 17–20, 1964.

South Bay Radiological Society
Secretary, Northern Section: Dr. John S. Wilson, 1515 Trousdale Dr., Burlingame, Calif.; Southern Section: Dr. A. C. Mitchell, 728 Cass, Monterey, Calif. Meets second Wednesday of each month.

South Carolina Radiological Society
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

Southern Radiological Conference
Secretary-Treasurer, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 4097, Mobile, Ala. Annual meeting: Grand Hotel, Point Clear, Ala., Jan. 31–Feb. 2, 1964.

Southwestern Radiological Society
Secretary, John M. McGuire, 904 Chelsea, El Paso, Tex. Meets last Monday of each month at 6:30 p.m. in the Paso del Norte Hotel.

Tennessee Radiological Society
Secretary, Dr. B. M. Brady, St. Joseph Hospital, Memphis, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas Radiological Society
Secretary, Dr. R. P. O'Bannon, 402 Professional Bldg., 1216 Pennsylvania Ave., Fort Worth 4, Tex. Annual meeting: Dallas, Tex., Jan. 31–Feb. 1, 1964.

Tri-State Radiological Society
Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Oct., Jan., March and May, 8:00 p.m., Elks Club in Evansville, Ind.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7:00 p.m. at University Hospital, Ann Arbor, Mich.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
Secretary, Dr. Richard Y. Card, St. Mark's Hospital, Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Vermont Radiological Society
Secretary, Dr. John R. Williams, 160 Allen St., Rutland, Vt.

Virginia Radiological Society
Secretary, Dr. John M. Ratliff, Mary Immaculate Hospital, Newport News, Va. Interim meeting: Homestead Hotel, Hot Springs, Va., April 24–25, 1964.

Washington State Radiological Society
Secretary, Dr. Robert H. Rosenberg, 7011 38th Ave., N.E., Seattle 15, Wash. Meets quarterly.

West Virginia Radiological Society
Secretary, Dr. Karl J. Myers, The Myers Clinic-Broaddus Hospital, Philippi, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

Westchester Radiological Society
Secretary, Dr. Edward T. Bello, Westchester Academy of Medicine, Section on Radiology, Purchase, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society
Secretary, Dr. Charles Benkendorf, 408 St. Francis St., Green Bay, Wis. Annual meeting each spring in various places.

CUBA, MEXICO, PUERTO RICO AND CENTRAL AMERICA

Asociación de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.
Secretary-General, Dr. Raul Arguello, 5a. Ave., Norte No. 48, San Salvador, El Salvador. Meets annually in a rotating manner in the six countries.

Sociedad de Radiología de El Salvador
Secretary, Dr. Rafael Vaga Gómez.

Sociedad de Radiología de Guatemala
Secretary, Dr. Carlos E. Escobar, 9ª. Calle A 0-05, Zona 1, Guatemala.

Sociedad de Radiología y Fisioterapía Cubana
Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

Sociedad Costarricense de Radiologia
Secretary, Dr. James Fernández Carballo, Apartado viii, San José, Costa Rica.

Sociedad Mexicana de Radiología, A. C.
Calle del Oro No. 15, México 7, D. F.
Secretary-General, Dr. E. Alvarez Hernández.
Meets first Monday of each month.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico
Secretary, Dr. Jorge Carreras Girard, Suite 504, Professional Bldg., Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 p.m. at the Puerto Rico Medical Association Bldg. in San Juan.

BRITISH COMMONWEALTH OF NATIONS

Association of Radiologists of the Province of Quebec
Secretary, Dr. R. Robillard, Notre-Dame Hospital, 1560 Sherbrooke St., East, Montreal, Que., Canada. Meets four times a year.

British Institute of Radiology
Honorary Secretary, Dr. R. D. Hoare, 32 Welbeck St., London, W. 1, England. Meets monthly from October until May.

Canadian Association of Physicists, Division of Medical and Biological Physics.
Honorary Secretary-Treasurer, Paul M. Pfalzner, Dept. of Therapeutic Radiology, University of Western Ontario, London, Ont., Canada. Annual meeting: Halifax, Nova Scotia, June, 1964.

Edmonton and District Radiological Society
Secretary, Dr. J. T. Mason, 540 Tegler Bldg., Edmonton, Alberta, Canada. Meets second Tuesday of each month, October to May.

Faculty of Radiologists
Honorary Secretary, Dr. C. J. Hodson, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting to be announced.

Faculty of Radiologists, Royal College of Surgeons in Ireland
Registrar, Dr. H. O'Flanagan, F.R.C.P.I., D.P.H., 123 St. Stephens Green, Dublin 2, Ireland.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 p.m. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1, England.

Canadian Association of Radiologists

Honorary Secretary-Treasurer, Dr. D. J. Sieniewicz, *Associate Honorary Secretary-Treasurer*, Dr. Maurice Dufresne 1555 Summerhill Ave., Montreal 25, Que., Canada. Annual meeting: Hotel Vancouver, Vancouver, B.C., Feb. 29–March 4, 1964.

Montreal Radiological Study Club

Secretary, Dr. Leonard Rosenthall, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

Section of Radiology, Canadian Medical Association

Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electro-Radiologie Médicale

General Secretary, Dr. Maurice Dufresne, 1560 Sherbrooke (East), Montreal, Que., Canada. Meets third Saturday each month.

Toronto Radiological Society

Secretary, Dr. Wallace M. Roy, St. Joseph's Hospitals, 30 The Queensway, Toronto 3, Ont., Canada. Meets second Monday of each month September through May.

College of Radiologists of Australia

Honorary Secretary, Dr. E. A. Booth, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

South America

Asociación Argentina de Radiología

Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

Ateneo de Radiologia

Secretary, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 P.M. in the Hospital Nacional del Centenario, Santa Fe 1300, Rosario.

Colégio Brasileiro de Radiologia

Secretary-General, Dr. Tede Eston de Eston, Caixa Postal 5984, São Paulo, Brazil.

Sociedad Argentina de Radiologia

Secretary, Dr. Armando B. de Onaindia, Santa Fe 1171, Buenos Aires. Meetings are held monthly.

Sociedad Bolivana de Radiología

Secretary, Dr. Javier Prada Méndez, Casilla 1596, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia

Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia

Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología

Secretary, Dr. J. P. Velasco, Avenida Santa María 0410, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia

Secretary, Dr. Alberto Mejía Diazgranados, Carrera 13, No. 25–31, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología y Fisioterapía

Secretary, Dr. Luis Blum, P.O. Box 3712, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología

Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiologia

Secretary, Dr. Vicente Ubillus, Apartado 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

Sociedad de Radiologia del Atlantico

Secretary, Dr. Raul Fernandez, Calle 40 #41–110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay

Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedade de Radiologia de Pernambuco

Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenologia y Medicina Nuclear de la Provincia de Córdoba

Secretary-General, Dr. Carlos A. Oulton, Santa Rosa 447, Córdoba, Argentina.

Sociedad Venezolana de Radiología

Secretary-General, Dr. Rubén Merenfeld, Apartado No. 9362, Candelaria, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft

President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Belge de Radiologie

General Secretary, Dr. S. Masy, 256 Chaussée de Wavre, Heverlee-lez-Louvain, Belgium. Meets in February, March, May, June, October, November and December.

Société Française d'Electroradiologie Médicale, and its branches: Socété du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.

Secretary-General, Dr. Ch. Proux, 9 rue Daru, Paris 8ᵉ, France.

Československá Společnost pro Roentgenologii a Radiologii

Secretary, Dr. Robert Poch, Praha 12, Šrobárova 50, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Deutsche Röntgengesellschaft

Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut., Lagenbeckstr. 1, Mainz, Germany.

Società Italiana di Radiologia Medica e di Medicina Nucleare

Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

Nederlandse Vereniging voor Radiologie

Secretary, Dr. H. F. O. Stricker, Schalklaar, Netherlands.

Scandinavian Roentgen Societies

The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Española de Radiología y Electrología Médicas y Medicina Nuclear

Secretary, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

Schweizerische Gesellschaft für Radiologie und Nuklearmedizin (Société Suisse de Radiologie et de Médecine Nucléaire)

Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

Asia

Indian Radiological Association

Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

Indonesian Radiological Society

Secretary, Professor Sjahriar Rasad Taman Tjut Mutiah 1, Djakarta, Indonesia.

ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

HEAD

BREZINA, K. Seltene intrakranielle Aneurysmen. (Rare intracranial aneurysms.) *Radiologia Austriaca*, 1963, *14*, 117–129. (From: Zentralröntgeninstitut des Kaiser-Franz-Joseph-Spitals der Stadt Wien, Vienna, Austria.)

An arteriosclerotic basis used to be considered as the most common cause of intracranial aneurysms. Current literature indicates that most of these aneurysms have a congenital etiology. Symptoms may be absent for a long time but clinical signs appear after a rupture of the aneurysm and depend upon the location and extent of the hemorrhage. Two patients are discussed and, as a co-incidence, each had sustained a cranial injury at 6 years of age.

The first patient, a boy of 17, complained of decreasing vision in the right eye for 6 years and he was known to have complete optic atrophy in the left eye for 3 years. A neurologic examination was otherwise essentially normal. An aneurysm, measuring 8.5 ×7.5 cm., was located at the bifurcation of the internal carotid on the left side. It had caused marked destruction of the sella turcica and partial erosion of the lesser wings of the sphenoid.

Another boy, 12 years of age, was hospitalized because of a temporary loss of consciousness following a second trauma to the skull. Neurologic signs were minimal and the optic fundi were normal. Roentgenographic examination showed a giant aneurysm arising from the basilar artery or one of its branches. Considerable thinning of the calvaria and marked increase in the digital impressions indicated an internal hydrocephalus, which required a Torkildsen drainage. The lesion measured 5.0 cm. in diameter and its extensively calcified wall was 6 mm. in thickness. It was situated in the region of the third ventricle with its major portion just to the right of the midline.—*J. Zausner, M.D.*

LYON, LEONARD Z., and SARNAT, BERNARD G. Limited opening of the mouth caused by enlarged coronoid processes: report of case. *J. Am. Dent. A.*, Nov., 1963, *67*, 644–650. (Address: 9735 Wilshire Boulevard, Beverly Hills, Calif.)

The authors report a case of bilateral general enlargement of the mandibular coronoid process causing definite limitation of mandibular movement because of impingement on the zygomatic bone in a 27 year old male symptomatic for 14 years. Laminagrams confirmed the diagnosis. Following resection of both coronoid processes through an intra-oral approach, a normal range of motion of the mandible was obtained and there were no complications or external scars.

Bilateral enlargement of the coronoid process producing limitation of mandibular excursion is an unusual condition but it must be added to the differential diagnosis of ankylosis of the mandible. An extensive classification according to cause is presented.

The etiology of enlargement of the coronoid process needs clarification. Several theories are explored and the possible relationship to osteochondroma of the coronoid process is discussed.—*Francis P. Shea, M.D.*

PASTREMOLI, A. Osservazioni radiologiche su alcuni casi di displasia fibrosa monostotica del mascellare superiore. (Radiologic observations on a few cases of monostotic fibrous dysplasia of the superior maxillary bone.) *Ann. radiol. diag.*, 1963, *36*, 278–302. (From: Istituto di Radiologia dell'Università di Bologna, and Reparto di Radiologia dell'Ospedale Civile di Imola, Italy.)

Four cases of monostotic fibrous dysplasia, in which the maxillary bone was involved, are presented. The patients' ages were 53, 69, 46 and 23 years, respectively. In 2 cases the antrum was also involved with obliteration.

In the discussion the author disagrees with the conclusions drawn by Lichtenstein and Jaffe on fibrous dysplasia. In his opinion the etiology of the process is either related to trauma or is of inflammatory odontogenous origin. It is also stated that roentgenologically it is not possible to differentiate monostotic fibrous dysplasia from fibroid osteoma of the maxillary bone, and that the pathologic changes could likewise be considered an incomplete form of the leontiasis ossea.

It is felt by this reviewer that the author does not support his conclusions with very definite roentgen and histologic findings.—*A. F. Govoni, M.D.*

WOLLIN, D. G. The os odontoideum: separate odontoid process. *J. Bone & Joint Surg.*, Oct., 1963, *45-A*, 1459–1471. (Address: 1206 Johnson Street, Kingston, Ontario, Canada.)

The os odontoideum is a developmental anomaly of the axis in which the odontoid process is divided by a transverse gap. The separate apical portion may form the articulation with the transverse ligament of the atlas and when this occurs the distal fragment provides inadequate stabilization for the atlas and dislocation at the atlanto-axial articulation may result. Lateral roentgenograms made in flexion and extension will demonstrate the dislocation to optimum advantage.

The author admits that it is not always easy to differentiate between an old ununited fracture of the odontoid and an os odontoideum. In the latter there is usually no history of a significant injury. Typically the os odontoideum is a small corticated ossicle separated from the base of the odontoid by a gap of varying width. The plane of cleavage is above the plane of the superior articular processes of the axis and the base of the odontoid may project upward as a peg or convexity. Often the anterior arch of the atlas is overdeveloped and the posterior arch is attenuated.

Nine such cases are presented and discussed. Only 2 had objective evidence of compression of the cervical cord. Pain and limitation of neck movements were the two most frequent symptoms. Medicolegally it is important not to mistake this condition for a recent fracture of the odontoid.—*Arthur E. Childe, M.D.*

Capurro, F. Garcia, Francois, R., and Sommerguten, G. (Montevideo, Uruguay). Encasquetamiento occipito-cervical: un signo radiológico de la artritis occipito-atloidea y atloido-axoidea. (Occipito-cervical telescoping: a radiologic sign of occipito-atloid and atloid-axis arthritis.) *Radiología*, Panamá, Dec., 1962, *13*, 11–14.

In arthritic disease involving the upper two cervical vertebrae, one can find in lateral roentgenograms a number of alterations: wedging of the bodies of the axis and atlas, loss of parallelism between occiput and atlas, osteoporosis or osteosclerosis of the odontoid, osteophytes of the anterior borders of atlas and axis, diastasis between the anterior border of the odontoid process and the posterior rim of the atlas, and partial or complete ankylosis of the occipito-atloid and atloid-axis joints.

In addition there is another valuable sign: the relationship between the tip of the odontoid process with Chamberlain's line. This line is drawn from the posterior border of the hard palate to the upper border of the lowermost part of the occipital fossa. The odontoid process tip normally is at or below Chamberlain's line; it may be found above this line in arthritis and arthrosis of the occipito-atloid and atloid-axis joints. The reason for it is that with degeneration of the articular cartilage the upper cervical spine telescopes itself into the base of the skull.—*Francisco Comas, M.D.*

Rickles, Norman H., and Joshi, Bhaskar A. (Portland, Ore.) A possible case in a human and an investigation in dogs of death from air embolism during root canal therapy. *J. Am. Dent. A.*, Sept., 1963, *67*, 397–404.

Air embolism occurs when air is introduced into the circulation at a greater pressure than that in the vasculature. The dangerous effect of these emboli depends upon: (1) the amount of air or gas (which varies from one type of animal to another) in volume per kg.; (2) the speed of its injection, the effectiveness of which is contingent on the relation of the size of the pulmonary vessels and branches to the body weight; (3) body position, with the left lateral being the safest; (4) nature of the gas injected, with the more readily soluble gases such as oxygen and carbon dioxide the least apt to be dangerous.

The authors relate an incident, discussed with them, of the death of a young dental patient which occurred just a few minutes after air had been used for several minutes to clean the root canals of the lower teeth. The degree of emphysema in the face of the youth led the pathologist to tie off the large vessels and open the right ventricle under water thus demonstrating a large quantity of air to be present. Magnin has reported one case and Shovelton several cases where subcutaneous emphysema of the cheek, lower eyelid, and the neck followed the use of pressurized air to clean the root canals from the central incisors to the second bicuspid.

In experimental attempts to reduplicate this, 7 dogs were subjected to controlled laboratory investigation using techniques varying the air pressure, the method of application of the air, the root canal of the specific tooth used, and the age of the animal. They were observed as to respiration and heart rate, with records of blood pressure and electrocardiograms kept in 3 cases. The experiment was continued for 30 to 40 minutes or until the animal died. Autopsies were conducted with the animals in the supine position.

Three animals survived the experiment, in 2 of which the air was blown intermittently into the root canal with no obstruction to the back flow of the air. The third animal was old, leading to the assumption that senile changes of thickened vascular walls, fewer periapical vessels and smaller apical canals discouraged the entrance of air into the vasculature.

All of the deceased had some degree of obstruction of the back flow of air from the root canal. They exhibited frothy blood in the right heart, air emboli in the superior vena cava, internal mammary vein, jugular vein, and coronary arteries with an enlarged heart and collapsed lungs.

It was deduced that the formation of emboli was enhanced by the obstruction to the back flow of the air. The passage of the small air bubbles was via the smaller veins to the jugular vein, thence to the right heart via the superior vena cava where they accumulated as frothy blood. With the animal in the sitting position, right lateral, or supine position, the out-flow of the right heart was superior in position to the bulk of the blood in the ventricle, thus allowing the frothy blood to accumulate in the area of the pulmonary valve and block the normal flow of blood. There followed an increase in the systemic blood pressure with a subsequent gradual decline, and pooling of blood in the right heart, and death. It was surmised that placing the patient on his left side would cause the pulmonary valve to be below the level of the blood in the right ventricle and allow a normal flow of blood from the right heart. This might be a life saving procedure in the event such occurrences were encountered. Subsequent studies with the dogs in a sitting position caused death in a few seconds rather than minutes.—*Sam W. Campbell, M.D.*

Keil, Rudolf, Randow, Friedrich, and Schulze, Hans-Arthur. Strontium 90 in Menschenzähnen. I. Mitteilung. (Strontium 90 in human teeth. Part I.) *Strahlentherapie*, June, 1963, *121*, 294–298. (From: Institut für Allgemein- und Kommunalhygiene der Universität, Rostock, Germany.)

A collection of teeth from humans aged 5 years and upward was measured radiochemically by the method recommended by Groos (using the report AERE HP/R2056). An average content of 0.55 pc Sr^{90}/g. calcium was found on the basis of the impulse-rate from the Y^{90} oxalate precipitate.—*Henry G. Moehring, M.D.*

Keil, Ruldolf, Randow, Friedrich, and Schulze, Hans-Arthur. Strontium 90 in Menschenzähnen. II. Mitteilung. (Strontium 90 in human teeth. Part II.) *Strahlentherapie*, Sept., 1963, *122*, 117–122. (From: Institut für Allgemein- und Kommunalhygiene der Universität, Rostock, Germany.)

The strontium 90 content of teeth from humans of different ages shows that contamination with Sr^{90} decreases after the second decade of life. The contamination rates for deciduous teeth for the year 1961 was 0.44 and 0.46 for the first half of 1962 (7 to 9 year old children). The contamination rates for permanent teeth of children up to 18 years old during these same years was 0.49 and 0.36, respectively; for adults between 18 and 30 years, 0.13 and 0.14; and for adults over 30 years, 0.10 and 0.05 pc Sr^{90}/g. calcium.

With an arbitrary "standard tooth" contaminated to an intensity of 0.5 pc/g. calcium and yielding 1 g. of ash with 36 per cent calcium, the Sr^{90} content is eight million atoms. These atoms undergo approximately 0.4 nuclear "events" per minute, therefore 25 per hour and 200,000 per year. If one assumes that the Sr^{90} is in equilibrium with Y^{90}, this rate is doubled.—*Henry G. Moehring, M.D.*

NECK AND CHEST

Falor, William H., Kelly, Thomas R., and Jackson, J. Bruce. Intrathoracic goiter. *Surg., Gynec. & Obst.*, Nov., 1963, *117*, 604–610. (From: Surgical Service, Akron City Hospital, Akron, Ohio.)

In the expanding literature, a goiter located in the thorax has been identified as intrathoracic, substernal, mediastinal, aberrant mediastinal, partial and total intrathoracic, plunging, posterior mediastinal, and anterior mediastinal. These titles, descriptive of anatomic location, fail to identify both the site or origin of the goiter and, of far more importance to the surgeon, the vascular attachments of the tumor. A goiter which originates in the neck and secondarily descends into the thorax will carry its cervical vascular attachments with it; a goiter which originates within the thorax may be expected to develop vascular connections to the adjacent intrathoracic vessels, or may, if associated with a cervical goiter, have a mixed intrathoracic-cervical blood supply.

Primary intrathoracic goiters must almost invariably be removed by the transthoracic approach, since it is impossible by the cervical route to ligate short vessels arising from the arch of the aorta or the adjacent large vessels. The authors report 1 primary intrathoracic goiter—posterior mediastinal; and 3 cases of mixed primary and secondary intrathoracic goiter—1 anterior and 2 posterior mediastinal.

Almost all secondary anterior and the majority of secondary posterior intrathoracic goiters may safely be removed through the standard cervical incision, while almost all primary intrathoracic goiters must be removed through a thoracotomy incision, commonly right posterolateral, occasionally transsternal. —*C. Peter Truog, M.D.*

Liebow, Averill A. Recent observations on pulmonary collateral circulation. *Med. Thoracalis*, 1962, *19*, 609–622. (Address: Yale University, New Haven, Conn.)

The production of collateral circulation encompasses the larger problem of angiogenesis. New observations indicate that chemical as well as mechanical forces must guide the development, growth, and destination of collateral vessels in the lung. Mechanical expansion of smaller vessels and capillaries is the first phase. However, nonmechanical guidance mechanisms are indicated when lung collaterals develop in an orderly fashion, so that arteries come to connect with arteries and veins with veins, although all are derived from a common capillary bed of granulation tissue. Hormonal control of this process has been shown in rats, where cortisone inhibits and growth hormone stimulates the process.

Once the collateral circulation is established in a lung, hemodynamics are altered. With an interrupted pulmonary artery, there is a transpulmonary left-to-left shunt. With developed collaterals, one may get a left-to-right shunt reversing blood flow into still patent pulmonary arteries. Connections between the high pressure systemic and low pressure pulmonary arterial system represent points of resistance which can increase the work of the right ventricle, and produce also a shunting of blood into normal tissue.—*Arch H. Hall, M.D.*

Sanders, Vernon. Idiopathic disease of myocardium: a prospective study. *A.M.A. Arch. Int. Med.*, Nov., 1963, *112*, 661–676. (Address: 6363 Roswell Road, Atlanta, Ga.)

The author reviews the clinical and pathologic features of idiopathic disease of the myocardium in 27 patients who had objective evidence of heart disease prior to age 45 in the absence of (1) angina or electrocardiographic evidence of arteriosclerotic heart disease, (2) pulmonary or systemic hypertension, (3) constrictive pericardial disease, and (4) organic heart murmurs suggesting acquired valvular lesions or congenital heart disease. The average age of this group was 36.6 years of which 78 per cent were males.

The signs and symptoms were predominantly those of compromised cardiac output. The intial complaints included easy fatigability, exertional dyspnea, late afternoon ankle swelling and palpitations. Six patients had evidence of embolic phenomena.

Chest roentgenograms revealed generalized enlargement of the cardiac silhouette, which often resembled pericardial effusion. Biopsies and CO_2 angiograms in 10 patients failed to reveal fluid in the pericardial sac suggesting that the abnormal cardiac shadow was probably due to a baggy, dilated, thickened myocardium. Fluoroscopy failed to show any discrete chamber enlargement. Myocardial contractions were termed "hypoactive," "shallow," and "feeble."

An infectious agent was searched for but was not found. Viral studies in 12 instances proved unrewarding. Other etiologic factors are discussed as well.

The concept of pancardiopathy is emphasized with pathologic studies showing endocardial and pericardial as well as myocardial involvement.

It is suggested that many examples of idiopathic disease of the myocardium may share a common inciting factor and may represent a burned-out stage of infectious myocarditis.—*Francis P. Shea, M.D.*

ABDOMEN

KISER, JOHN R. Chronic gastric ulcer associated with aspirin ingestion: a report of 5 cases and review of the literature. *Am. J. Digest. Dis.*, Oct., 1963, *8*, 856–869. (Address: 2290 Sixth Avenue, San Diego, Calif.)

The author states that his attention was directed toward the subject of chronic gastric ulcer in patients with long standing pain and aspirin ingestion when several patients were seen with these complaints in rapid succession. None of the patients being reported was taking other ulcerogenic drugs at the time the ulcer was discovered.

In experimental work on rats in 1937, Barbour and Dickerson found that aspirin given in toxic doses by the oral route produced superficial gastric ulceration in 66 of 69 rats. Subcutaneously given aspirin also caused gastric ulceration, and in larger doses caused severe gastric hemorrhage. Douthwaite and Lintott, in 1939, described gastric irritation and gastric hemorrhage in patients following the use of aspirin. They examined 16 patients given 1 gm. of crushed aspirin in 28 cc. of water. It was found that 13 of these patients developed a reaction of the mucosa varying from hyperemia to intense congestion with submucous hemorrhages. During the past 10 years a number of references have been made to the occurrences of massive gastrointestinal bleeding following the ingestion of aspirin. Brown and Mitchell, in 1956, studied 46 patients hospitalized with massive gastrointestinal bleeding; 70 per cent of these had ingested aspirin within several hours prior to the hemorrhage, while 40 per cent of 100 control patients without bleeding had aspirin during the same period. Watson and Pierson, in 1961, found occult blood in the stools of patients using enteric-coated tablets, and suggested that perhaps the small intestine was also a site of bleeding.

Douglas and Johnston, in 1961, studied 78 patients hospitalized with chronic gastric ulcer; 57 of these patients had been taking salicylates for an extended period. They noted that many of these patients were headache sufferers with pain symptoms predating the ulcer. Observation of this clinical triad of chronic relapsing headache, aspirin ingestion, and chronic gastric ulcer was the initial stimulus for their study. They also suggested, however, that in view of the enormous quantities of aspirin consumed by people in general, it must be selective in its propensity to cause ulcer. They point out that patients who are seen with a gastric ulcer should be questioned specifically concerning the ingestion of salicylates, especially aspirin, as information about such a common drug would not ordinarily be volunteered.

The author presents 5 cases of chronic gastric ulcer, each associated with the ingestion of a large amount of salicylates prior to the onset of symptomatology and discovery of the ulcer. Each of these individuals had a benign, chronic pain problem. Healing of the ulcer took place only after discontinuation of the salicylates.—*Douglas S. Kellogg, M.D.*

BOCHETTO, JOSEPH F., RAYCROFT, JOHN F., and DE INNOCENTES, LOUIS W. Multiple polyposis, exostosis, and soft tissue tumors. *Surg., Gynec. & Obst.*, Oct., 1963, *117*, 489–494. (From: Department of Surgery, Kings County Hospital Medical Center, Brooklyn, N. Y.)

The triad of polyposis of the colon, multiple osteomatosis, and multiple soft tissue tumors was first described by Gardner and his co-workers in 1950 and is known as Gardner's syndrome. They presented 6 patients in a family group of 51 living persons and also postulated a dominant mode of inheritance for all 3 manifestations passed via a single defective gene.

Bone tumors. The osseous tumors are benign osteomatosis or exostosis. They arise primarily in membranous bone and are confined for the most part to the skull and facial bones. These tumors are generally self limiting, and none have been reported to undergo malignant change.

Soft tissue tumors. They are usually mutiple, most frequently cutaneous or subcutaneous. The commonest forms are epidermoid cysts, desmoid tumors, fibromas, neurofibromas, or poorly differentiated connective tissue tumors. Leiomyomas, fibrosarcomas and multiple lipomas have also been reported. Except in rare cases, these soft tissue tumors appear not to have a malignant potential.

Multiple polyposis. The intestinal form of this disease is preponderantly within the colon, and the natural course of the colonic involvement, with its severe malignant change, is essentially the same in both diseases. As can be seen then, the colonic manifestation is by far the most common component of this triad.

The authors present a case of Gardner's syndrome in a 34 year old woman and 2 cases of the disease in offsprings of the patient, each of whom has 2 stigmata of the syndrome, namely, osteomatosis of the facial bones and ribs and soft tissue fibromas. Although the 2 offsprings have remained free from colonic disease until the age of 19 and 21, if Gardner's thesis is correct, colonic polyposis should eventually develop. The bony tumors and soft tissue lesions precede the clinical diagnosis of polyposis and constitute an important early diagnostic finding in this entity.—*J. T. Ling, M.D.*

Garbsch, H. Die unblutige röntgenologische Funktionsdiagnostik der extrahepatalen Gallenwege. (The bloodless, roentgenologic, functional diagnostic examination of the extrahepatic biliary pathways.) *Radiologia Austriaca*, 1963, *14*, 131–158. (From: Medizinische Universitätsklinik in Wien, Vienna, Austria.)

The conventional methods of cholecystography (oral or intravenous) or operative choledochography including planimetric or volumetric measurements, cannot give adequate information about the function of the extrahepatic bile ducts. A combination of pharmacologic tests and serial roentgenograms is necessary for a satisfactory study of the physiologic and pathophysiologic function of the biliary tract. The effects of several pharmaco-dynamic tests are indicated in the following table:

Morphine, a parasympathetic stimulant, produces an effect opposite to that of atropine and amylnitrite. The results of the cholecystokinin test indicate that it exerts its effects over humoral rather than neurologic pathways.

A diagnosis of the precise type and location of a disturbance in function within the biliary tract is of great importance, particularly if surgical intervention is contemplated. The author gives a detailed account of his investigations of the varied forms of dyskinesias because in a report of 1,100 cholecystectomized patients, 25 per cent of the gallbladders showed no pathology, either on gross or histologic examination. The dyskinesias and the effect of cholecystokinin (CCK) are as follows:

(1) *Hyperkinesia* (hyperkinetic dyskinesia; hyperkinetic type; hyperevacuation; hypermotility; vesicular hypertonicity; hypertonic cholecystopathy). After the administration of CCK, there is a rapid and marked decrease in the diagonal diameter of the gallbladder, the contraction-quotient being 1.7 to 4.3 (with an average of 2.54). CCK acts directly on the muscularis of the gallbladder, producing marked contraction of the viscus, while the choledochal sphincter is in a normal or in a relaxed state.

(2) *Hypokinesia* (hypotonia of the gallbladder; hypotonic dystonia; hypokinetic form; atonic type; cholecystatony; atonic distention; atonic cholecystopathy). After CCK, there is a delayed and minimal decrease in the duodenal diameter and only a contraction-quotient of 1.0–1.5 (average is 1.23). The intensity of opacification in the hepatic and common ducts is increased as a result of increased spasm of the sphincter of Oddi.

(3) *Hypertonicity of the sphincter of Oddi* (hypertonic dyskinesia; hypertonic dystonia; spasm of the sphincter). The isolated form of this disturbance is rare and usually occurs only in females under 35 years of age. CCK produces a very minimal decrease in the diagonal diameter of the gallbladder, the quotient being 0.9 to 1.3 or similar to hypokinesia. The gallbladder fills very early and rapidly; the intrahepatic portions of the bile ducts are normal in caliber and completely opacified; the hepatic and common ducts are distended. After a fatty meal, the size of the gallbladder is minimally decreased. The behavior of the

	Gallbladder	Sphincter of Oddi	Duct of Wirsung
Morphine	Increased tonus: Gallbladder is normal in size or dilated	Increased tonus: Bile flow is reduced	Increased tonus: Reflux is reduced
Atropine and Amylnitrite	Decreased tonus: Gallbladder is enlarged	Decreased tonus: Bile flow is increased	Decreased tonus: Reflux is greater
Cholecystokinin	Increased tonus: Gallbladder is smaller	Decreased tonus: Bile flow is increased	Decreased tonus: Reflux is greater

sphincter after CCK serves to differentiate a functional disturbance from an inflammatory process or an organic stenosis of the papilla, since evacuation of the gallbladder would exclude the possibility of an organic lesion.

(4) *Hypertonicity of the gallbladder neck-cystic duct portion* (dyskinesia of the neck-cystic duct type; evacuation insufficiency of the infundibulum; syphopathia). After CCK, the diameter of the gallbladder is greater, so that the quotient is almost always less than 1.0; the viscus assumes a conical shape but if evacuation is poor or absent, the gallbladder becomes almost spherical. Atropine-amylnitrite cannot produce any evacuation of the gallbladder contents when a disturbance in function exists. CCK, in larger doses, may cause partial evacuation. Morphine is contraindicated in this type.

(5) *Hypotonicity of the sphincter of Oddi* (hypotonic dyskinesia of the sphincter). This type is common after cholecystectomy. The usual measurements are unsatisfactory. The condition is recognized by the poor filling of the extrahepatic biliary system (and the gallbladder, if present) due to flow of contrast material into the duodenum in spurts. Cineroentgenography demonstrates a prolonged opening phase of the sphincter and diminished closure time. Morphine produces a rapid and complete filling of the biliary system. In questionable cases, the administration of CCK causes widening of the papilla and unhampered evacuation of the gallbladder.

While CCK offers valuable information, an analysis of functional disturbances cannot be considered complete without the other aids, especially cineroentgenography. CCK also has its limitations, particularly in women during the menstrual phase, pregnancy or menopause, since the hormonal effect during these periods is not clearly understood.—*J. Zausner, M.D.*

Blood and Lymph System

Abrams, Herbert L. Present status of biplane cineangiocardiography: a roentgenographic procedure. *J.A.M.A.*, June 8, 1963, *184*, 747–752. (From: Department of Radiology, Stanford Medical Center, 300 Pasteur Drive, Palo Alto, Calif.)

The value of biplane study in defining more precisely anatomic and physiologic findings in angiocardiography led to the early use of coupled rapid exposures in 2 planes and by 1955 biplane cinefluorography was feasible. The addition of image intesifiers synchronized and triggered by their respective cameras in a time sequence exactly 180° out of phase so that the tubes were activated alternatingly provided a more useful tool as previously described. A 35 mm. negative, later printed on 16 mm. film, is used, originally with an 11 inch and now with a 9 inch image intensifier in recording injection sequences at sites selected with the aid of previously collected data. The sequences start with the injection of the contrast material and are monitored with electrocardiographic control.

The use of this technique in 300 clinical studies of the heart is summarized.

In left to right shunts it allows definition of a shunt not otherwise detected through routine catheterization studies either because of the small size of the shunt or the masking of a shunt at one level by a shunt at another. The details of the shunt may be demonstrated.

In the Taussig-Bing anomaly immediate opacification of the transposed aorta occurs simultaneously with shunting into the pulmonary artery, where the diluting effect of concomitant left ventricular ejection may be noted.

In Ebstein's anomaly gross tricuspid insufficiency is obvious and the contraction of the atrialized portion of the right ventricle may be seen to be in unison with the functioning right ventricle.

In aortic valvular and subvalvular disease observation of the dynamics allows determination of constancy of the site as in organic obstruction; visualization of obstruction may remain throughout systole as in functional infundibular stenosis or may be a transient protodiastolic event of no significance. A jet during systole, of contrast material being ejected or of ejected blood impinging upon the contrast material, as well as valvular deformity allows detection of valvular stenosis. Direct visualization of regurgitation in aortic insufficiency enables a quantitative approach in the evaluation of the reflux. Mitral stenosis displays a large left atrium with diminished amplitude of contraction and limited valvular motion. Evaluation of the jet through the narrowed valve permits rough quantification. In mitral insufficiency there is direct visualization of the event which must be distinguished from that occurring physiologically following prolonged diastole by observing several cycles.

In endocardial fibroelastosis there is left sided dilatation and marked damping of systolic contraction along with prolonged lesser circulation time because of increased left sided pressures.

Biplane cineangiocardiography has not only proved its value in the investigation of virtually all congenital and acquired heart lesions but provides a valuable tool in physiologic research. In left to right shunts at the atrial level, the major shunt occurs during early filling, and at the ventricular level the shunt, which is confined to systole in small defects, gains an increasing diastolic component with larger defects, augmented by rising left atrial systole. In right to left shunts, right ventricular systolic ejection occurs into the aorta directly and there is a right to left ventricular shunt during protodiastole, followed by little shunting during the rest of diastole. Aortic insufficiency has been noted in dogs during protodiastole with moderate injection pressures and quantities. The reflux ceases with valve closure and is augmented by increased intrathoracic pressure. Many other problems have been brought into sharper focus with this technique.—*Dr. Fredrick L. Mishkin M.D.*

CHASE, N., HASS, W. K., and RANSOHOFF, J. Modified method for percutaneous brachial angiography. *A.M.A. Arch. Neurol.*, June, 1963, *8*, 632–639. (Address: Dr. Norman E. Chase, New York University-Bellevue Medical Center, 550 First Avenue, New York 16, N. Y.)

A safe, rapid method of percutaneous brachial angiography designed for use in a program of pancerebral angiography is presented. The method differs from other reported methods of brachial angiography mainly in the type of needle employed, the site of puncture and the use of isotonic saline floating on top of the contrast agent in the syringe.

The method consists of mild sedation prior to injection and local infiltration anesthesia about the site of arterial puncture. In both right and left brachial angiographies, a blood pressure cuff is placed below the elbow. After palpation, the brachial artery in the mid-upper arm is located and punctured with a 2½ inch No. 15 or 16 gauge "thin-walled" Cournand needle. The needle is threaded as far as possible up the artery, then taped in place and connected to a pressure injector pre-loaded with 20 to 30 cc. of contrast agent and 15 to 20 cc. of isotonic saline floating on top of the contrast agent in the syringe. The blood pressure cuff is inflated above systolic pressure and the injection is made with the injector set at 625 lb. of pressure. Timing, synchronization and positioning vary with the area to be examined.

This method has been used on more than 300 vessels in 200 consecutive patients. Right brachial injection produces visualization of the right carotid and right vertebral arteries in all cases where the vessels are present and not occluded. In 40 per cent of patients the extracranial portion of the left carotid artery is visualized and in approximately 20 per cent, the intracranial branches of the left carotid artery are reported to be adequately visualized. The left vertebral artery is best visualized by left brachial angiography. When it is necessary to visualize the left carotid artery, it is necessary in most cases to perform a standard percutaneous puncture of the left common carotid artery.

The complications included: (1) some discomfort in the face and shoulder immediately after injection; (2) lost radial pulse, in 3 of a total of 5 cases returning after a short time; (3) transient increase in neurologic deficit in 2; and (4) one death 5 days after injection. —*Sam. B. Baker, M.D.*

PHILP, T., SAMUEL, ERIC, and DUNCAN, J. G. Reversed vertebral artery blood flow in subclavian artery obstruction (subclavian steal). *Clin. Radiol.*, July, 1963, *14*, 310–316. (From: Radiodiagnostic Department, Royal Infirmary, Edinburgh, Scotland.)

Stenosis or occlusion of the subclavian artery proximal to its four main branches (vertebral, internal mammary, costocervical and thyrocervical) may reduce the effectiveness of the collateral circulation to the arm unless refilling of the main vessel can be achieved by reversed flow in one or more of the main branches. If as a result of proximal subclavian artery stenosis, a fall in pressure distal to the stenosis below that at the vertebral basilar junction occurs, there may follow a reversal of the pressure gradient in the vertebral artery, producing symptoms of ischemia. This is thought to be due to diversion of blood from the cerebral circulation to the upper limb.

The commonest site of subclavian artery thrombosis is distal to the origins of the major branches, and collateral circulation to the arm is via the intercostal arteries and the suprascapular and subscapular vessels. Thrombosis proximal to the origin of the major branches may result in refilling of the main channel through any or all of the major branches. Following thrombosis at the origin of the subclavian artery, an adequate supply of blood to the affected area through collateral channels may prevent the onset of signs and symptoms of peripheral ischemia, but this may be at the expense of the cerebral circulation. Cerebral symptoms may not ensue if compensatory flow to the brain proves adequate, but atherosclerosis which is a generalized disease may retard such compensatory flow. As atherosclerosis progresses, the effects of decreased cerebral flow may become more evident.

Three cases are presented illustrating reversal of blood flow in a vertebral artery following occlusion or stenosis of the corresponding subclavian artery proximal to the origin of the vertebral artery. Retrograde filling of other collateral vessels, particularly the thyrocervical and costocervical trunks has been demonstrated in one case, and the anatomy of the total possible collateral circulation to the arm is discussed.—*Samuel G. Henderson, M.D.*

GARBSCH, H., KAINDL, F., KAUTEK, E., and ORELLI, A. V. Diagnostische Problematik bei venöser Stauung im Schulter-Hals-Bereich. (Diagnostic problems of venous stasis in the shoulder-neck area.) *Radiologia Austriaca*, 1963, *14*, 67–76. (From: Medizinische Universitätsklinik in Wien, Vienna, Austria.)

The most frequent causes of venous stasis of the shoulder-neck area are phlebothrombosis, traumatic thrombosis, venous obstruction due to scar formation, tumors and other extraneous causes of compression. Venous angiography is essential to determine the site of obstruction and the extent of the collateral circulation. It is contraindicated, however, in the presence of acute infection, and when a thromboembolic tendency exists. Five pertinent cases are reported.

In the first two patients, the axillary vein was obstructed and ample collateral circulation had been established. In the third patient, a swelling of the left arm, extending upward to the shoulder and neck, had developed suddenly following a venipuncture. Four months later, angiography disclosed an obstruction of the distal segment of the axillary vein with collateral circulation. The fourth patient was a forester, age 52, with a history of sudden swelling of the right arm without trauma. Five months later phlebography revealed extension of the arm veins to the supraclavicular and neck veins. Other veins led to the scapular veins which also were connected with the neck veins. In the fifth patient, a phlebogram revealed obstruction of the left axillary vein. Of special interest was the presence of tissue strands which connected the first rib with the undersurface of the clavicle. When these strands were severed surgically, a complete cure ensued.

Slow development of axillary vein obstruction suggests compression, while a sudden onset denotes thrombosis. When collateral circulation is absent, cardiac catheterization is advisable to test the degree of patency of the vein. Etiologic factors cannot be established in all cases with certainty, but constitutional factors like strong muscles, dropping shoulders and skeletal anomalies favor the venous stasis. Immediate causes are faulty neurovascular regulation and sudden increase of endovascular coagulation of blood which occasionally follows repeated minute traumatic episodes.—*Ernest Kraft, M.D.*

Lang, Erich K. A survey of the complications of percutaneous retrograde arteriography: Seldinger technic. *Radiology*, Aug., 1963, *81*, 257–263. (From: Department of Radiology, Methodist Hospital, Indianapolis, Ind.)

By means of a questionaire sent to 300 physicians, data were obtained regarding the complications encountered in 11,402 arteriographies performed by the Seldinger technique. The reported complications were classified as minor, serious, or fatal. The type and relative frequency of the various complications are shown by appropriate tables.

There were 325 complications classified as minor. In this group the main lesions were local hematoma and subintimal or intramural injection of contrast substance. Practically all these patients also had temporary arterial spasm and loss of pulse. Minor complications were usually related to faulty technique. Of the 81 complications classified as serious, arterial thrombosis at the puncture site was the most common and most dreaded. Disease of the cardiovascular system was apparently a factor predisposing to thrombosis. Appropriate therapy, when started early, will have a favorable influence on the morbidity and mortality rate of the serious complications, especially arterial thrombosis.

There were 7 fatalities recorded. It would appear that they were due mainly to arterial thrombosis or rupture, or to pulmonary infarction. One of the deaths could have been due to the contrast medium but it was felt that this type of complication is rarely encountered.—*McClure Wilson, M.D.*

Simon, Harold, Moquin, Ross, and Dameshek, William. The inferior venacavagram and lymphoproliferative disorders. *J.A.M.A.*, June 22, 1963, *184*, 978–980. (Address: Dr. H. Simon, 171 Harrison Avenue, Boston 11, Mass.)

The inferior vena cava was opacified by injection of contrast medium into the right or left femoral vein. Valuable information was obtained in regard to extent of disease and localization of tumor. This proved a valuable guide to radiation therapy. Routine excretory urograms were made following the examination. The inferior vena cavagram yielded more information than the excretory urogram.

A total of 21 cases were studied with 12 abnormal inferior vena cavagrams and 5 abnormal intravenous urograms.—*Conrad B. Frydenlund, M.D.*

Viamonte, Manuel, Jr., Altman, Donald, Parks, Raymond, Blum, Edward, Bevilacqua, Michael, and Recher, Louis. Radiographic-pathologic correlation in the interpretation of lymphangioadenograms. *Radiology*, June, 1963, *80*, 903–916. (From: Departments of Radiology and Pathology, University of Miami School of Medicine, Jackson Memorial Hospital, Miami, Fla.)

Lymphangioadenography has been used as an aid in differential diagnosis, evaluation of malignancies, causes of edema, and to stain the lymph nodes when later surgery is to be done. FDC Blue #1 dye was employed for lymph channel indentification, and ethiodol to inject the channels. Large bore catheters and an automatic pressure-temperature controlled injector have helped solve the technical problems of lymphangiography.

There were 253 successful lymphangiographic studies done. The characteristic findings of the normal lymph nodes, acute lymphadenitis, granulomas, metastatic malignancy, and lymphomas are described. Several of these are illustrated with reproductions of lymphangiograms and photomicrographs of histologic sections; particularly interesting are those of cat scratch disease, infectious mononucleosis, tuberculous adenitis, sarcoidosis, and histoplasmosis.

The conclusions are that abnormal morphology does not always indicate malignancy; different processes may show the same pattern; and the same pathologic process may show a varying pattern. When a large number of cases have been studied, a characteristic lymph node pattern may then be established.—*James C. Moore, M.D.*

SCHAFFER, BURTON, KOEHLER, P. RUBEN, DANIEL, C. RICHARD, WOHL, GEORGE T., RIVERA, ERNEST, MEYERS, WAYNE A., and SKELLEY, JOSEPH F. A critical evaluation of lymphangiography. *Radiology*, June, 1963, *80*, 917–930. (From: Departments of Radiology and Pathology of the Philadelphia General Hospital, and from the School of Veterinary Medicine of the University of Pennsylvania, Philadelphia. Pa.)

Lymphangiography was performed in 141 patients, with lesions divided into groups: (1) lymphovascular, (2) inflammatory, (3) lymphoma and (4) carcinoma. Histopathologic study was done in 41 cases, on 259 lymph nodes. The ethiodol globules in the lymph nodes were noted to be surrounded by giant cells as early as 12 hours after injection. Ethiodol was present early in the lung alveolar capillaries, later in the macrophages, and absent after several months. It was seen in the kidneys but without evidence of microinfarction or inflammation. It was also found in the spleen, but apparently without reaction. Repeat lymphangiograms showed no evidence of damage to the lymphatic system. Water soluble media were tried but were not satisfactory. Brilliant Blue Dye was used to identify the lymphatics.

Thirteen wound infections were noted; 1 patient had lymphangitis; other complications included fever (7), pain (2), vomiting (1), lymphatic rupture and extravasation without untoward effects (27), and swollen extremities (7). Pulmonary oil embolization occurred in 24 patients, including 1 with frank signs of pulmonary infarction. There was one intravenous injection, also without untoward effects. Studies are under way using ethiodol tagged with I^{131}, and isolation of tumor cells during lymphangiography.

It is felt that the procedure is of value in the diagnosis of lymphoma but of less value in diagnosing metastatic carcinoma. No permanent tissue damage has been demonstrated by histologic examinations, repeat studies, or by clinical evaluation.—*James C. Moore, M.D.*

GENERAL

LODWICK, GWILYM S., KEATS, THEODORE E., and DORST, JOHN P. The coding of roentgen images for computer analysis as applied to lung cancer. *Radiology*, Aug., 1963, *81*, 185–200. (From: Department of Radiology, University of Missouri School of Medicine, Columbia, Mo., and Department of Radiology, University of Iowa College of Medicine, Iowa City, Iowa.)

The increasing complexity of medical knowledge has prompted the search for more effective means of handling the vast amount of data used in modern patient care. The digital computer has proved valuable in performing this function in business and in many scientific disciplines, and can be equally useful in medicine, providing that roentgenographic data can be converted into the exact qualitative and quantitative forms required by the computer. The authors describe a concept of converting visual images on roentgenograms into numerical sequences which can be manipulated and evaluated by a digital computer.

For this study, the roentgenograms of 541 cases of primary lung cancer were reviewed and analyzed along with all known clinical information. Less than 1 per cent of the total number were lost to follow-up. In this series, the absolute 5 year survival rate was noted to be 1.3 per cent and was lower than that of several other large series of reported cases. This figure likely represents the advanced stage of the disease at the time of referral. In order to analyze a period in which the yield of survivals is relatively large, the 1 year survival was selected, for reasons which are discussed.

In the authors' method various individual characteristics of the tumor were selected for data analysis and each characteristic was quantitated in order to reflect adequately the extent of the disease process. This information was then assigned to specific numerical columns on a tabulating card. The interested reader should refer to the original article for a more detailed account of the data presentation. The accuracy of this detailed descriptive system was tested by reconstruction of the original roentgenographic appearance, utilizing only the numerical data from the card. Four such reconstructions are presented which reproduced the original in a highly satisfactory manner.

The computer-derived results of this study indicate that distinctly delineated, small tumors with little secondary involvement have much better survival and operability rates than the larger, less well outlined lesions with many secondary changes. It is suggested from this study that lung cancers are essentially uniform in their degree of malignancy. Another interesting feature of this analysis indicates that a location in the right middle lobe carries the poorest prognosis, as compared to other lobes, and that spherical tumors carry a better prognosis than elongated tumors. Calcification was noted to be rare in tumors of the mid or peripheral zone of the lung but was present in 14.5 per cent of tumors involving the hilar zone. In all cases the calcification was nonspecific and it was assumed that the tumors enveloped healed granulomatous lesions.

The authors emphasize that their principal objective is to present clearly a method of "digitizing" roentgenograms by which the data, converted into numerical sequences, can be studied by high speed data processing systems. This coding technique provides a basis for the exploration of the use of the digital computer in diagnostic radiology and for further evaluation of the roentgen examination as a means of predicting cancer behavior. It is obvious that a computer can produce no results which are better than the data it is given to process. Therefore, a requirement of "computer medicine" is that we learn to express our observations in precise terminology which can be recorded, processed electronically, and reproduced in a usable form.—*E. B. Best, M.D.*

Meyers, Phillip H., Becker, Hal C., Sweeney, James W., Nice, Charles M., Jr., and Nettleton, Wilson J., Jr. Evaluation of a computer-retrieved radiographic image. *Radiology*, Aug., 1963, *81*, 201–206. (From: Tulane University School of Medicine, New Orleans, La.)

An evaluation of computer-retrieved radiographic images is presented. This pilot study has convinced the authors: (1) that the present state of the electronic and mechanical art is entirely adequate to effect analog signal representation of radiographs and (2) that currently available analog-to-digital converters and interfaces for digital computers are entirely adequate.

The electronic system used in this study was designed and built by one of the authors. With a low-resolution system, 35 mm. reproductions and small segments of radiographs were electronically scanned, using a standard Tektronix type 535-A oscilloscope as a flying spot scanner raster source. The light from the scanning raster, after transilluminating the radiograph or film, was collected by a photomultiplier to develop a video signal which was D.C.-amplified and fed to an analog-to-digital converter. This digital information was sensed by an IBM 1401 digital computer through its Serial Input-Output Adapter. The elements of each horizontal line were then transferred to digital magnetic tape. The absolute values of the directional derivatives taken with the 1401 computer in the +X direction, and the +Y direction were summed for each area element. This new image matrix, which they called the composite derivative of the original image, was written on digital magnetic tape, and is being used in a computer analysis program for scanned radiographic images.

Both the original image and the derivative image were retrieved in two ways: (a) on the IBM 1403 printer to produce a gray scale and (b) with a simple digital-to-analog converter operating from the Serial I/O adapter of the IBM 1401 computer into an amplifier which modulated the Z axis of a cathode-ray tube in a standard oscilloscope with a long persistence screen—for visual observation. The oscilloscope was photographed with a Polaroid camera to produce permanent retrieved photographs of the original image and also of the derivative image.

The radiographic images retrieved from the digital computer afforded information below the threshold of visualization of the human eye on the original radiograph. Operational systems should be assembled to test pattern recognition and "computer diagnosis" hypotheses. This should result in the development of new and useful techniques.—*A. W. Sommer, M.D.*

RADIATION THERAPY

Burr, R. C., MacKay, E. N., and Sellers, A. H. Radiation therapy in the treatment of carcinoma of the lung. *Canad. M. A. J.*, June 15, 1963, *88*, 1181–1184. (Address: Dr. R. C. Burr, Professor of Radiotherapy, Queen's University, and Director, Ontario Cancer Treatment and Research Foundation, Kingston Clinic, Kingston, Ontario, Canada.)

From 1938 to 1958, 2,457 cases of cancer of the lung were treated at the Ontario Cancer Clinics. During part of this time only orthovoltage roentgen therapy (200–250 kvp.) was available but later cobalt 60 beam therapy was provided.

It was possible to compare the one year survival rates for cobalt 60 and roentgen therapy. Cobalt 60 beam therapy appears to have a significant advantage: 26 per cent as against 13 per cent in over 800 cases in each group.

Resection alone gave a one year survival rate of 54 per cent (50 cases), resection with radiation therapy 63 per cent (135 cases), radiation therapy alone 19.5 per cent (1,863 cases), and no therapy 8.6 per cent (409 cases). The five year survival rate for all methods was 3.8 per cent.—*Henry J. Klos, M.D.*

Haylock, Alan. Angiography in Kaposi's sarcoma. *Clin. Radiol.*, July, 1963, *14*, 304–309. (From: Department of Radiology, University College Hospital, Ibadan, Nigeria.)

The object of this paper is to report the angiographic findings in 7 cases of Kaposi's sarcoma in Nigerian patients, and to describe a technique in which diagnostic angiography is combined with chemotherapy.

In recent years it has been found that the tumor occurs frequently in Africa, being more common in moist tropical regions than in drier, sandy areas. It is seen 15 to 20 times more often in men than in women, especially in middle-aged patients. The etiology is obscure. The appearances are variable but characteristic, beginning with inflammation and vascular dilatation, and progressing through a granulomatous stage to actual neoplasia. The skin eruption is characterized by nodules and plaques of a bluish, bluish-red, or reddish-brown color, usually found on the extremities as tender and painful lesions. They may be discrete or coalescent, ranging in size from 1 mm. to 1 cm. in diameter. In most cases the underlying limb bones are affected, showing rarefaction, cyst formation, cortical erosions, and occasionally complete bone destruction. Visceral lesions are found most commonly in the intestines, followed by the liver and lungs.

Angiography is of value in Kaposi's sarcoma (1) to confirm the diagnosis, and (2) to demonstrate the true extent of the lesions often shown to be considerably greater than thought on clinical grounds. The contrast medium should be injected as quickly as possible and a larger quantity than usual should be used. There is much earlier visualization of the venous phase, and consequently the timing of the roentgenographic exposures must be altered.

On the roentgenograms each nodule is seen to receive a large blood supply from a single arterial vessel which breaks up into a leash of small interwoven vessels. The appearance of multiple vascular tumors in the subcutaneous tissues leads to an almost certain diagnosis of Kaposi's sarcoma. In multiple small congenital arteriovenous fistulae the clinical history and the patient's age will suggest the correct diagnosis, and this can be confirmed by biopsy.

Surgery is a suitable form of therapy when there are single isolated lesions. In more widespread involvement radiation therapy appears to be preferable to surgery. As an alternative to radical surgery cancer chemotherapy is being used increasingly in Nigeria because radiation therapy is not available. The drug of choice at present is a freshly dissolved solution of mustine hydrochloride B.P.C. in normal saline, containing 1 mg./cc. A dose of 20 mg. per limb has been used, repeated at intervals, if necessary. All of the 7 patients here reported who have been so treated are well at present, but true assessment of the results must be deferred until a longer time elapses. Roentgenologically, re-examination after chemotherapy shows that there does not seem to be any change in previously existing bone lesions, but the vascularity of the affected area is seen to be reduced. Many of the lesions previously demonstrated will be seen to have disappeared, while the others are reduced in size.—*Samuel G. Henderson, M.D.*

PAPILLON, J., DARGENT, M., and CHASSARD, J. L. La lymphographie au lipiodol ultrafluide en cancérologie (à propos de 62 observations). (Lymphography with ultrafluid lipiodol in cancerology [on the basis of 62 observations].) *J. de radiol., d'électrol. et de méd. nucléaire*, June–July, 1963, *44*, 397–406. (From: Chaire de Radiologie et Centre Léon-Bérard, Lyon, France.)

Lymphographic studies were performed in 62 cases, of which 2 were of an upper extremity; the remaining 60 were on the lower extremities, with 57 being bilateral and 3 unilateral; 12 per cent were technical failures.

Primary diseases of the lymph nodes, gynecologic and testicular tumors provided the bulk of cases, although miscellaneous lesions including cat-scratch disease and filiariasis are listed.

The authors conclude that primary malignant lymph node diseases, notably Hodgkin's disease, constitute indications for lymphography because of the prognostic information and therapeutic guidance obtained. As to uterine and cervical carcinoma, the lack of opacification of the presacral and promontorial lymphatic chains (which is expected by present methods) is a definite handicap.

Valuable as lymphography is, the skill and time required, and persisting uncertainties of interpretation preclude its use as a routine procedure.—*Frank A. Riebel, M.D.*

RIDER, W. D. Radiation damage to the brain—a new syndrome. *J. Canad. A. Radiologists*, June, 1963, *14*, 67–69. (From: Ontario Cancer Institute, Toronto, Ontario, Canada.)

Radiologists have long been aware of the fact that brain damage may follow exposure to ionizing radiation. Since nerve cells have been considered to be relatively radioresistant, it has been assumed that the necrotic changes in the neural tissue occur secondarily as the result of radiation injury to the more susceptible vascular tissues. Typically, there is a long latent period between the exposure to the radiant energy and the development of clinical signs and symptoms which, in the classic syndrome, gradually increase to a plateau and then persist. Tissue repair and recovery are not anticipated.

In recent years, investigators have begun to question the role of vascular damage in the pathogenesis. In some instances changes in the myelin sheath have been seen to precede the alterations in the cells of the vascular endothelium and the histologic pattern of a demyelinating disorder was thought to be produced by primary neural damage.

The author describes the clinical and pathologic findings in 3 patients treated for neoplasms of the middle ear with a cobalt 60 source to a depth dose of 5,500 rads administered over a one month period. An unusual syndrome evolved; symptoms appeared more quickly and were of shorter duration than those observed in the classic pattern. The latent period was measured in weeks, not months. The onset was acute, not gradual. Two patients recovered and the pathologic features were those of a demyelinating disease, not a vascular disorder.

Clinical evidence of postradiation brain damage first appeared about 10 weeks after completion of the radiation treatment and was characterized by nausea and vomiting followed by ataxia, dysarthria and dysphasia. There were signs of gross cerebellar ataxia. One patient suffered paralysis of the sixth cranial nerve and exhibited an extensor plantar response. There was no papilledema and the spinal fluid, electroencephalograms and ventriculograms were normal. One patient died 4 weeks after the onset of symptoms; the others began to improve at this time and recovery was complete in about 6 to 8 weeks. They remained well for 6 years.

Postmortem study of the brain revealed patchy, disseminated demyelination very similar to that seen in multiple sclerosis except that the plaques were confined to those portions of the cerebrum, cerebellum and brain stem which had received irradiation. Plaques were more numerous where the tissue dose was highest, but some were also present in areas of relatively low dosage. The pattern was strikingly different from that usually seen following radiation injury in that vascular damage was minimal and normal neurones and axones were seen passing through areas of demyelination.

The pathogenesis is open to speculation. Some of the features suggest an allergic or auto-immune response. Recent work indicates that certain cytoplasmic enzymes may be depressed by irradiation of nerve cells but that these changes are reversible.

The observations are important because they indicate that neural tissue is not uniquely insensitive to radiation. Brain damage occurs primarily and is not dependent upon vascular injury. The clinical picture differs radically from the previously accepted pattern. Therefore, it constitutes a new syndrome which must be recognized by the practitioner who might otherwise assume that the acute onset of neurologic signs and symptoms so soon after treatment was caused by tumor. In these circumstances, the author advises a "watch and wait" policy since the syndrome may regress spontaneously.—*Jack Reynolds, M.D.*

Graham, John B., and Villalba, Rafael J. Damage to the small intestine by radiotherapy. *Surg., Gynec. & Obst.*, June, 1963, *116*, 665–668. (From: Gynecologic Service, Roswell Park Memorial Institute, Buffalo, N. Y.)

The authors review their 6 cases of small intestine damage incidental to radiation therapy and review the principles of diagnosis and management based on these and other cases reported in the literature.

Most patients with radiation damage to the small intestine have received external radiation therapy with doses of 4,500 r or more to large fields, are thin, and usually have had previous surgery and/or sepsis in the pelvis presumably leading to adhesions fixing the bowel. Most complications occur in the first year after therapy and involve the terminal ileum.

The manifestations are: 1) obstruction, usually progressive; 2) perforation with peritonitis, abscess or fistula formation; 3) hemorrhage; and 4) diarrhea and malnutrition.

In general, conservative surgery with a by-pass procedure is recommended, such as ileo-transverse colostomy. Resection of the damaged, matted mass of intestine is tolerated poorly except in those cases where a very localized area of bowel may have been damaged by radium placement.—*Henry J. Klos, M.D.*

Mayer, E. G. Lokale Strahlenschäden—Ursachen und Folgerungen. (Local radiation damages, their causes and sequelae.) *Radiologia Austriaca*, 1963, *14*, 3–27. (From: Zentral-Röntgeninstitut der Universität in Wien [Guido-Holzknecht-Institut], Vienna, Austria.)

Radiation damage of the skin in orthovoltage and supervoltage therapy is frequently unavoidable and acceptable to a certain degree. Strangely enough, however, skin damage from an overdose of radiation occurs more frequently in the treatment of benign conditions, such as warts and syringomyelia. Excessive fluoroscopy, conducted by surgeons during fracture setting, is another cause. Such skin damage, however, is completely avoidable when proper precautions are taken as time monitoring, careful shutter control and frequent interruptions of fluoroscopy.

When such precautionary measures are followed, much permanent skin damage can be prevented. This was proved by the Vienna's Unfallskrankenhaus, where from 1925 until 1962 approximately 300,000 roentgen examinations had been performed without causing a single instance of radiodermatitis. Frequently, damage was cumulated by ultraviolet and hot-air treatments, by sunburns, irritating ointments and other harmful medications. The author also points out that therapeutic cortisone injection into the damaged skin may result in sloughing and ulcer formation, similar to pressure effect from braces and belts.

Other causes of radiodermatitis are excessive dosage due to faulty meters, inadequate monitoring devices and lack of shielding of large fields. Calibration of the roentgen-ray equipment should be done by an approved physicist at least every 3 years with meters checked by the Bureau of Standards.

In crossfire technique, faulty centering of the roentgen beam may result in a double dose due to the overlapping of two adjacent fields. Idiosyncrasy, so often blamed for unsuspected skin burns, does not exist. Increased radiosensitivity, however, occurs in the presence of nerve damage to an extremity. Therefore, syringomyelia must be ruled out prior to radiation therapy. Other causes of hypersensitivity are toxic dermatitis from medication in areas previously irradiated, obese abdominal wall and pendulous breasts.

Cooperation between the referring physician and the radiotherapist is frequently inadequate. Thus, a clinician without proper training and experience may prescribe an excessive dose. Also, a radiotherapist may be supplied with the misleading diagnosis of a possible malignancy and consequently cause permanent skin damage unnecessarily.

Numerous pertinent cases are discussed, partly from a medicolegal standpoint. Of special interest is the case of a martyr with a 50-year follow-up study. The patient was a technician who in "pioneer" days had received excessive radiation to her legs during fluoroscopies.—*Ernest Kraft, M.D.*

Krokowski, E., and Ehling, U. Strahlengefährdung, Strahlenschäden und Strahlenschutz des Auges. (Radiation dangers, radiation damages and radiation protection of the eye.) *Radiologia Austriaca*, 1963, *14*, 57–65. (From: Strahleninstitut und Strahlenklinik der Freien Universität Berlin am Städtischen Krankenhaus Westend und Max-Planck-Institut für vergleichende Erbbiologie und Erbpathologie, Berlin-Dahlem, Germany.)

The eye, as a superficially lying organ, is directly exposed to external radiation. Therefore, protection of this vital organ is important. To determine the radiosensitivity of the different parts, eyes of experimental rabbits were exposed to superficial roentgen rays. The technical factors were 60 kv., 4 ma., 4 cm. distance and 2 cm. diameter field.

The retina proved to be the least sensitive part, as no pathologic changes were noted with doses up to 3,000 r. Damage, however, was evident due to radiation-induced hydrophthalmus. The cornea was also radioresistant with doses up to 2,000 r. The eyeball had a weight loss of 12 per cent with 1,000 rads and of 40 per cent with 2,000 rads in the young, while in the adult animals the weight loss ranged only from 0.3 per cent to 2 per cent. The bony structures of the orbit showed retarded development with growth arrest in the young. The lens was the most sensitive part of the eye. With a single dose of 200 r development of a cataract started. With a protracted-fractionated dose of 1,000 r lens clouding could be observed in the adult.

From a practical standpoint one has to differentiate between (1) occupational hazards, especially of watch makers handling radioactive luminous dials, (2) the hazards of contaminated atmosphere and (3) the specific dangers from therapeutic irradiation of tumors. The accumulated dose of watch dial workers to the eyes is 70 r per year. Roentgenologists, whose daily average fluoroscopies are 2 hours, receive an annual dose of 8 to 16 r per year in spite of adequate precautions.

In view of the radiation hazards, adequate protection of the eyes is important. With conventional roentgen diagnostic procedures the dosage is still within normal limits. In roentgen therapy, however, when the orbital area is included in the field of radiation, leaded glass cups are essential to protect the lens and other contents from permanent damage. To assure the roentgenologist's safety during fluoroscopic examinations, the lead glass, covering the screen, must have a prescribed thickness. Also, the period of fluoroscopic studies should not exceed 2½ hours daily.

Of special importance are strict regulations in the workshops for luminous paints. Here, the workers' minimum age should be 18 years. The maximum period of continuous employment should not exceed 8 years, and under no circumstance should the cumulative radiation dose to the eye exceed 250 r. Not only medical but also ophthalmologic check-ups at regular intervals are essential to insure the safety of the exposed workers.—*Ernest Kraft, M.D.*

RADIOISOTOPES

TUBIANA, M., VALLÉE, G., and MABILLE, J. P. L'iode radio-actif et le cancer de la thyroïde. II. Intéret thérapeutique (à propos de 109 cas traités entre 1949 et 1958). (Radioactive iodine and thyroid carcinoma. II. Therapeutic value [on the basis of 109 cases treated between 1949 and 1958].) *J. de radiol., d'électrol. et de méd. nucléaire,* June–July, 1963, *44,* 381–396. (From: Département des Radiations de l'Institut G.-Roussy, et Laboratoire des Isotopes de l'Hôpital Necker, Paris, France.)

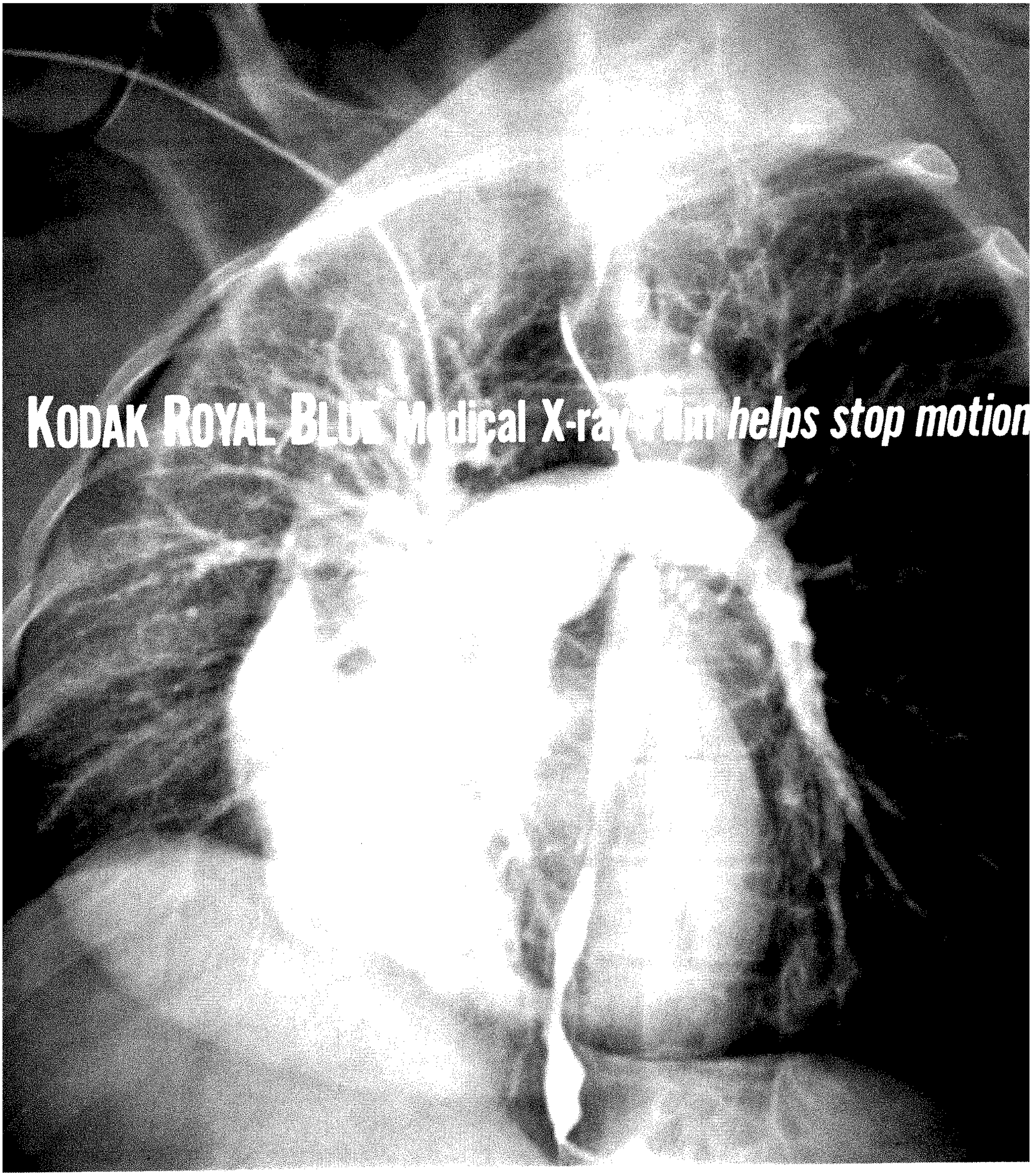
Among more than 300 patients studied and tested for thyroid carcinoma, 109 received one or more therapeutic doses of radioactive iodine between 1949 and 1958; the periods between the end of the treatment and publication are from 3 to 12 years.

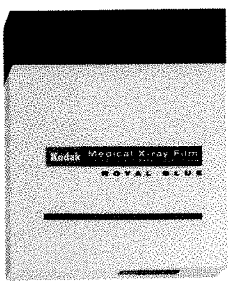
It is known that thyroid carcinomas lose, in whole or part, the functional activity of the normal gland; therefore, irradiation with isotopes is less selective. It is advisable to submit to treatment only those carcinomas which are able to take up iodine in sufficient concentration. Histopathology plays an important role, the more differentiated and colloid-bearing tumors being more suitable for I^{131} therapy, although it is impossible to make selection on histopathology alone. External gammagraphy and histoautoradiography of punch biopsies or surgical material are valuable aids. The latter method is more useful since in external determinations confusion may arise between interpretation of normal and tumorous tissues.

Of the treated cases, 54 had no metastases, many in spite of incomplete surgical exeresis; there were numerous 5 year survivors. Fifty-five cases had metastases of which 28 were in lung, 24 in bone, and 3 in both. The survival rate was better in the metastatic cases where ability to fix iodine was demonstrated. Of the 25 patients with iodine-fixing metastases who were treated 5 years ago or more, 13 have survived, including 3 whose lesions disappeared at least 10 years ago.—*Frank A. Riebel, M.D.*

BRÜCKNER, L., ČERNÝ, J., and BEŠKA, F. Our experience with cobalt beam unit GUT-CO-400-2. *Radiol. clin.,* 1963, *32,* 142–151. (Address: Dr. L. Brückner, Oncological Department, Paskov, Č.S.S.R., Czechoslovakia.)

In 1960 a Soviet cobalt 60 beam therapy unit of "400 radium gram-equivalents" was installed in the authors' hospital. They describe their experience with 169 patients and come to conclusions which agree with what they had read in the world literature.—*Henry J. Klos, M.D.*





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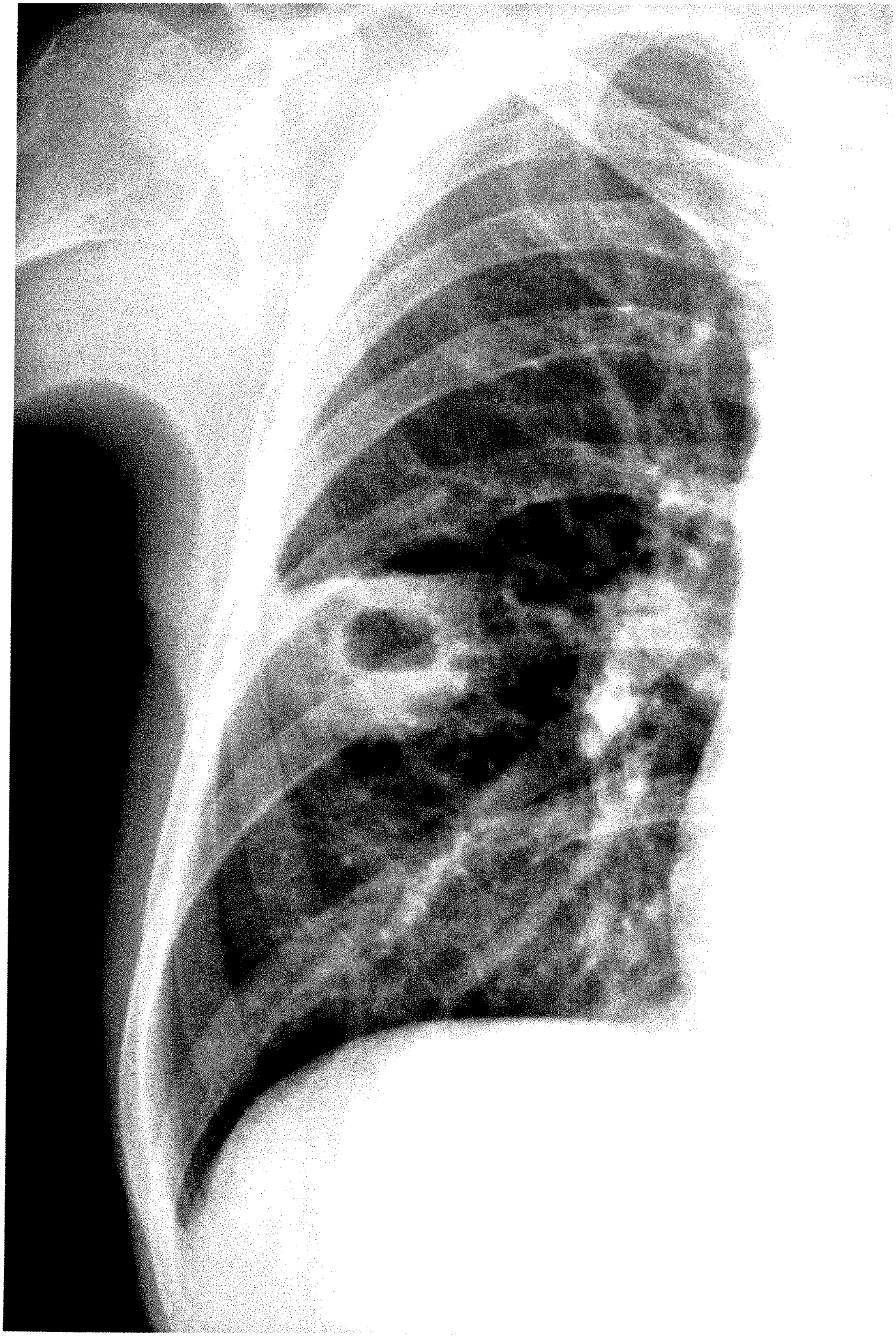

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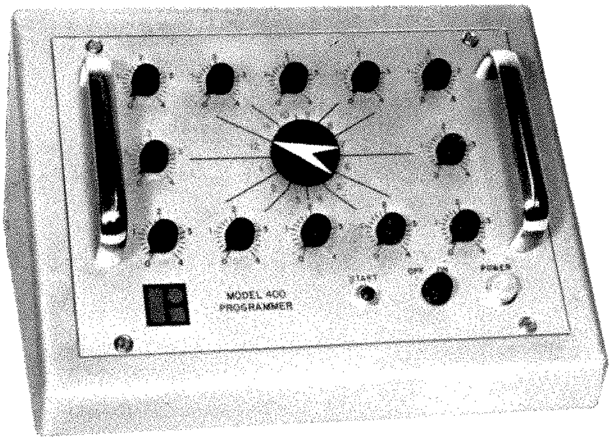

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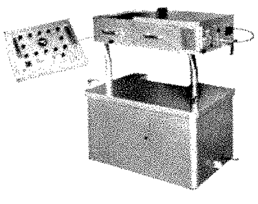

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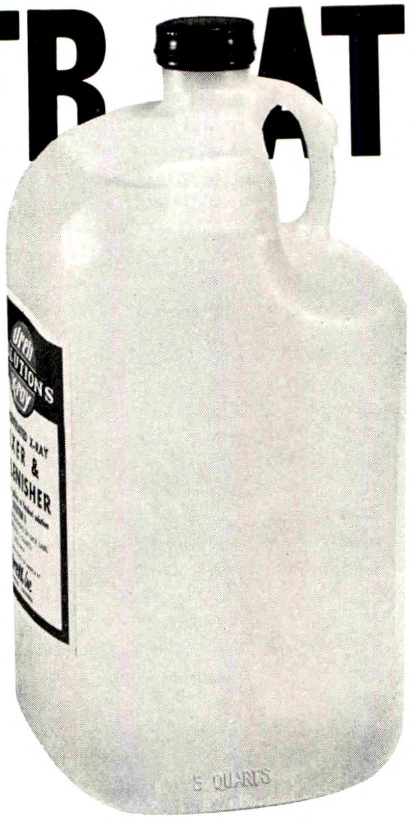

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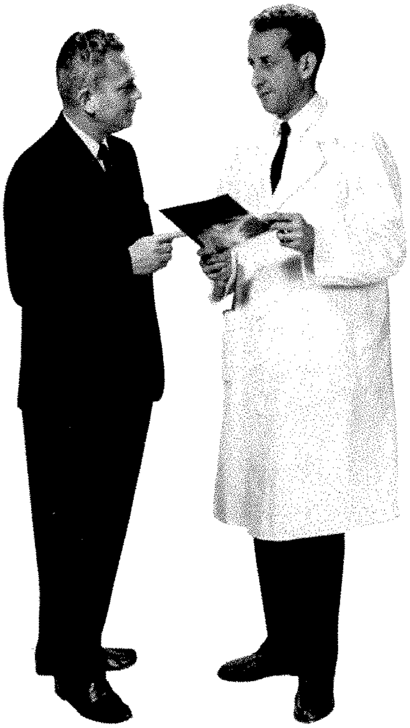

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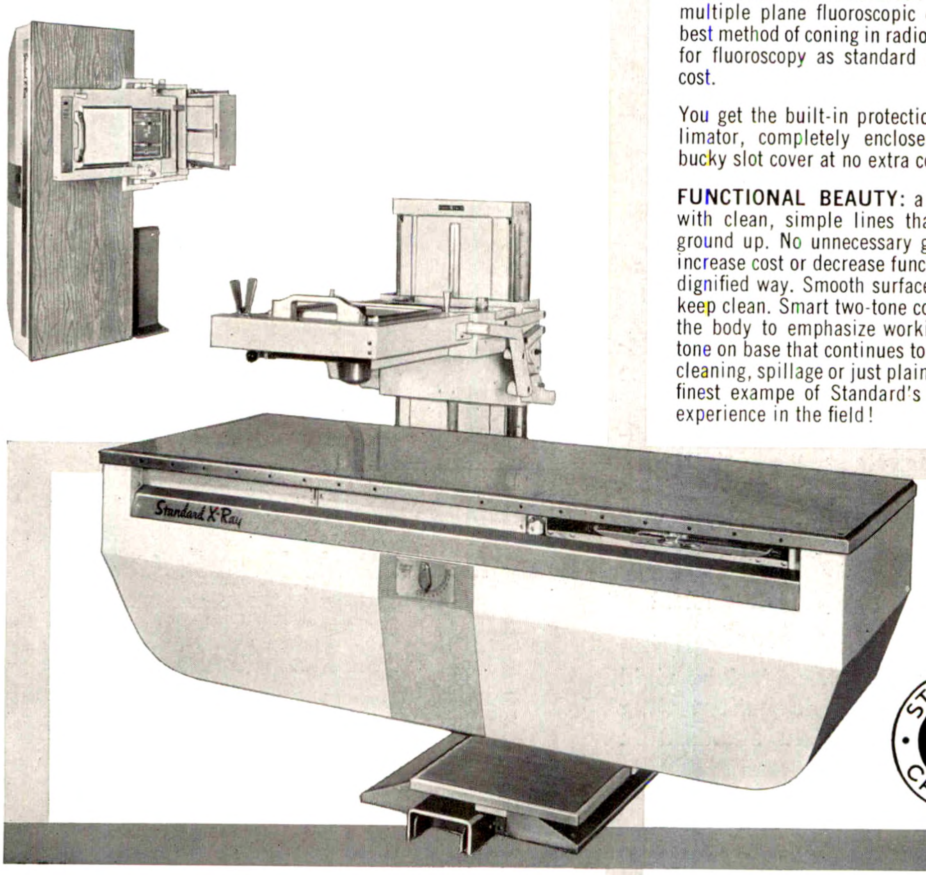

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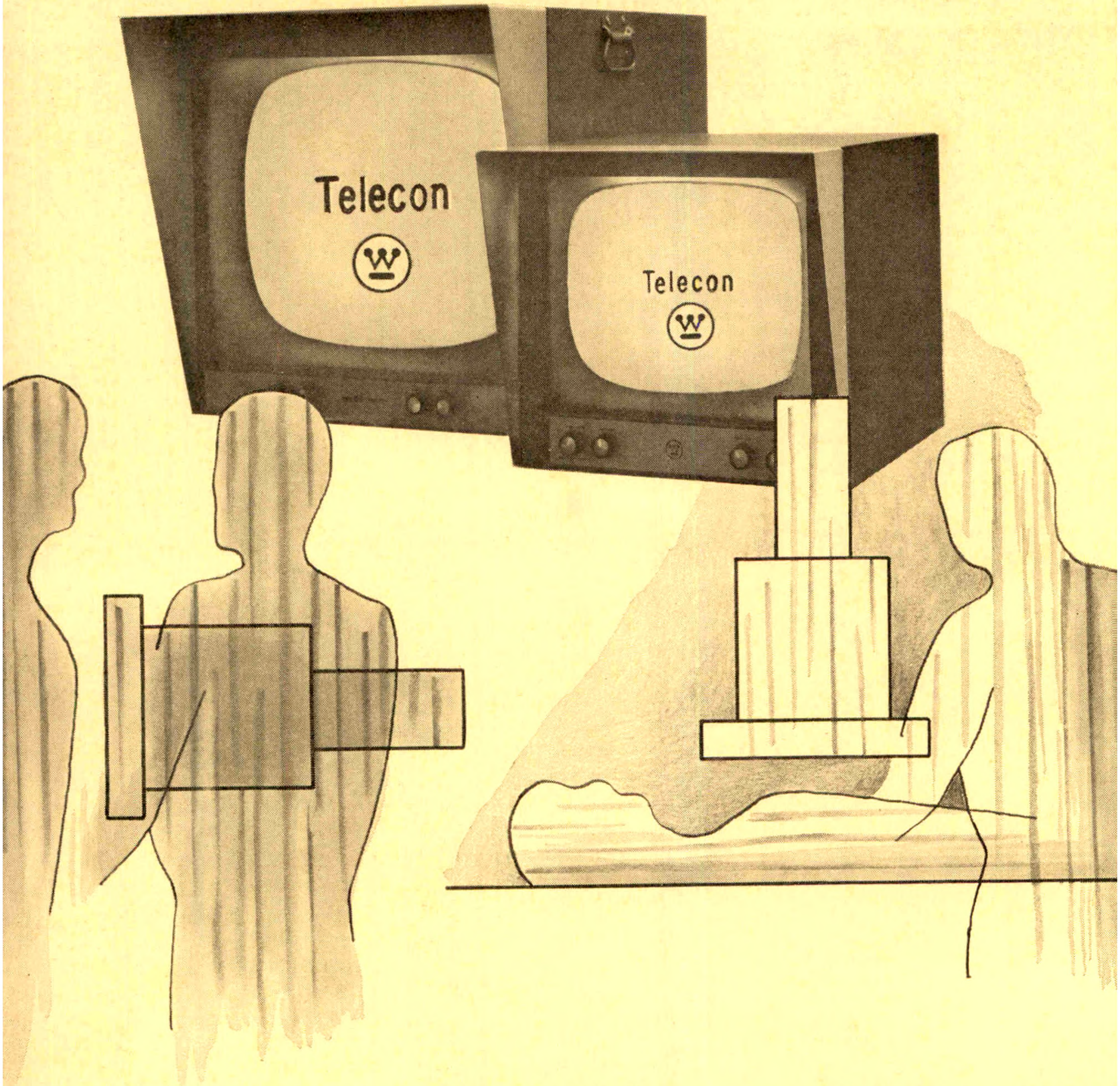

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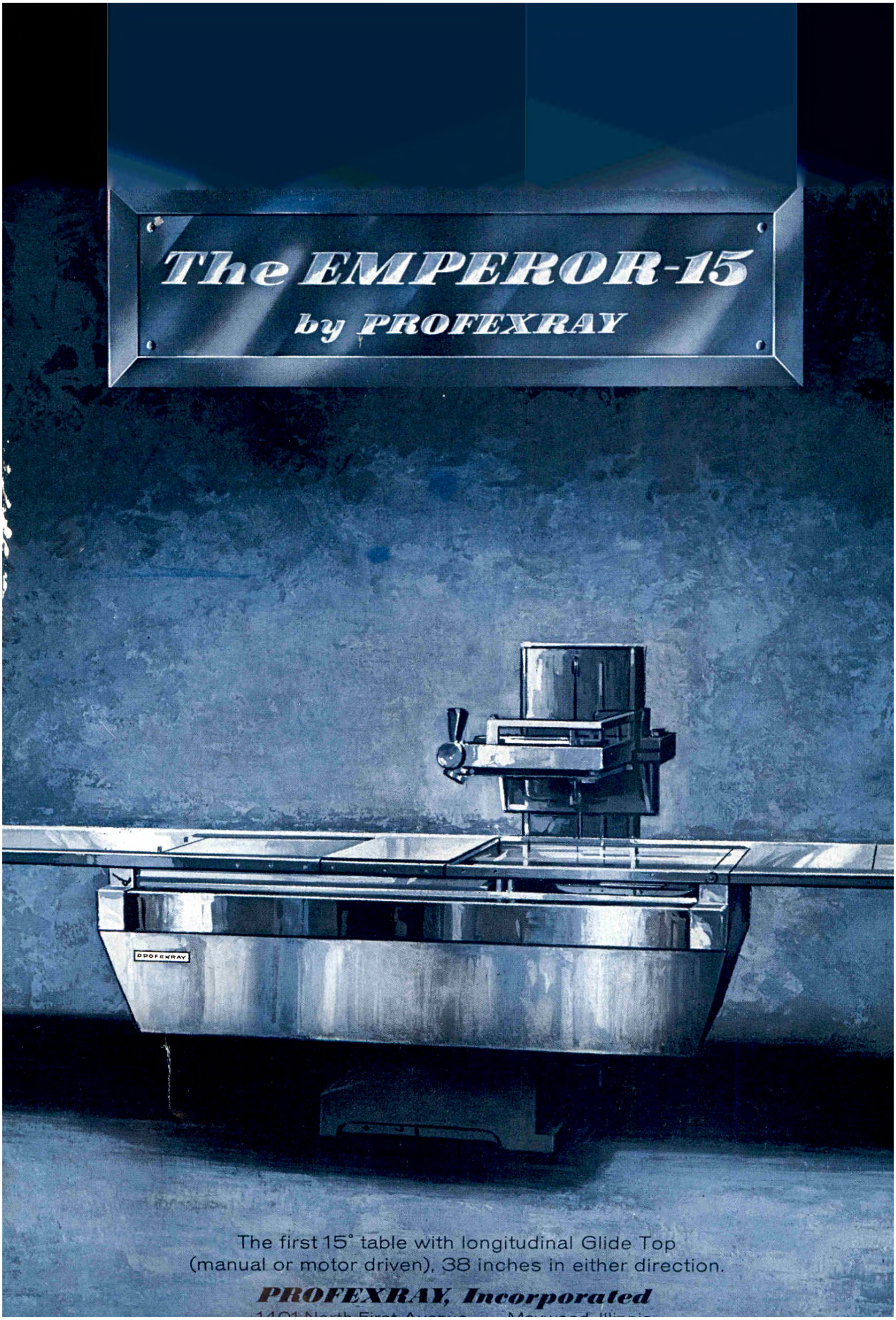

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References: (1) Richter, K., et al.: Deutsche Gesundh. *15*:630 (Mar. 24) 1960. (2) Saltzman, G. F.: Acta radiol. *54*:417 (Dec.) 1960. (3) Whiteside, C. G.: Brit. J. Radiol. *33*:124 (Feb.) 1960. (4) Brannan, H. M., et al.: Proc. Staff Meet. Mayo Clin. *36*:197 (Apr. 12) 1961. (5) Kemp, F. H., and Wright, F. W.: Brit. J. Radiol. *34*:63 (Jan.) 1961. (6) Saltzman, G. F., and Sundstrom, K. A.: Acta radiol. *54*:353 (Nov.) 1960. (7) White, W. W., and Fischer, H. W.: Am. J. Roentgenol. *87*:745 (Apr.) 1962.

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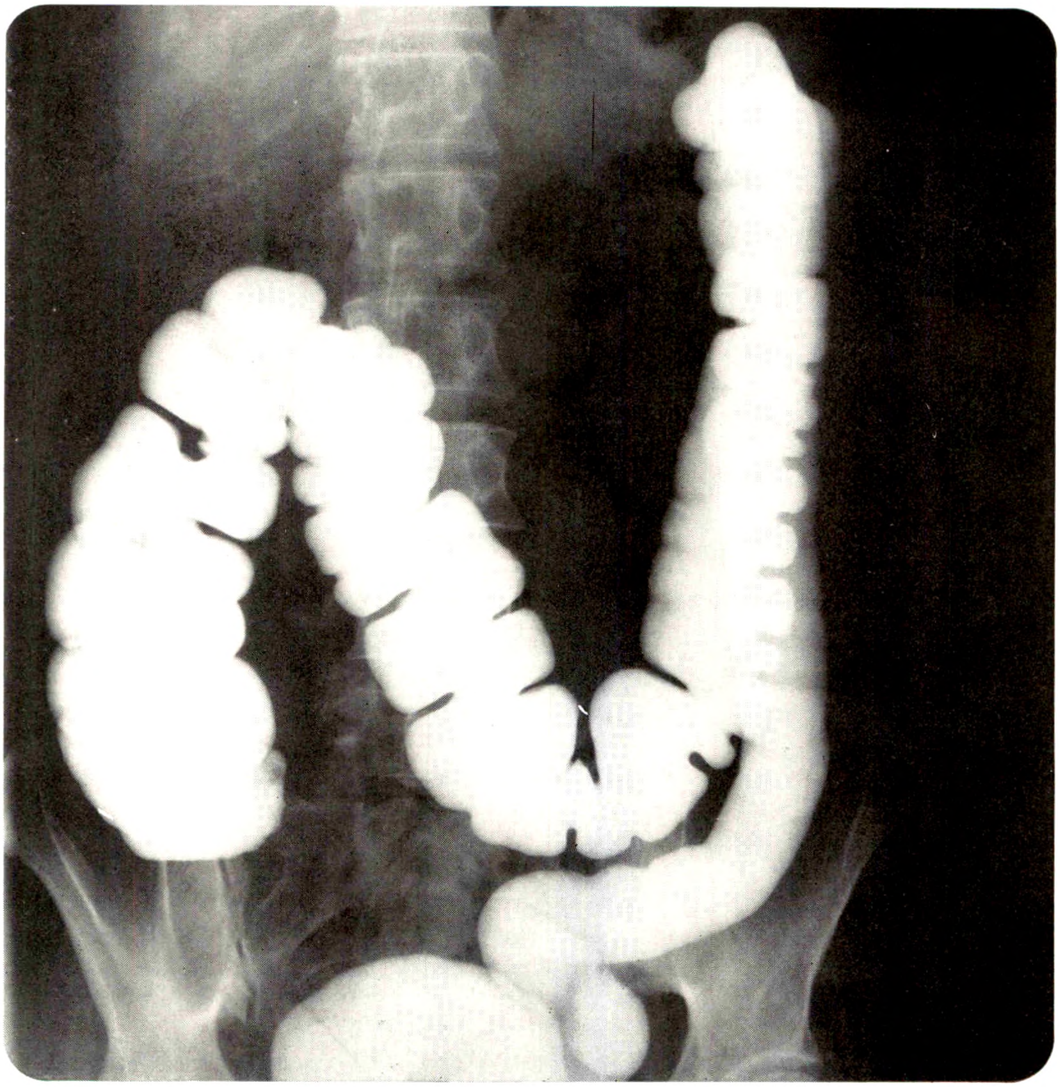

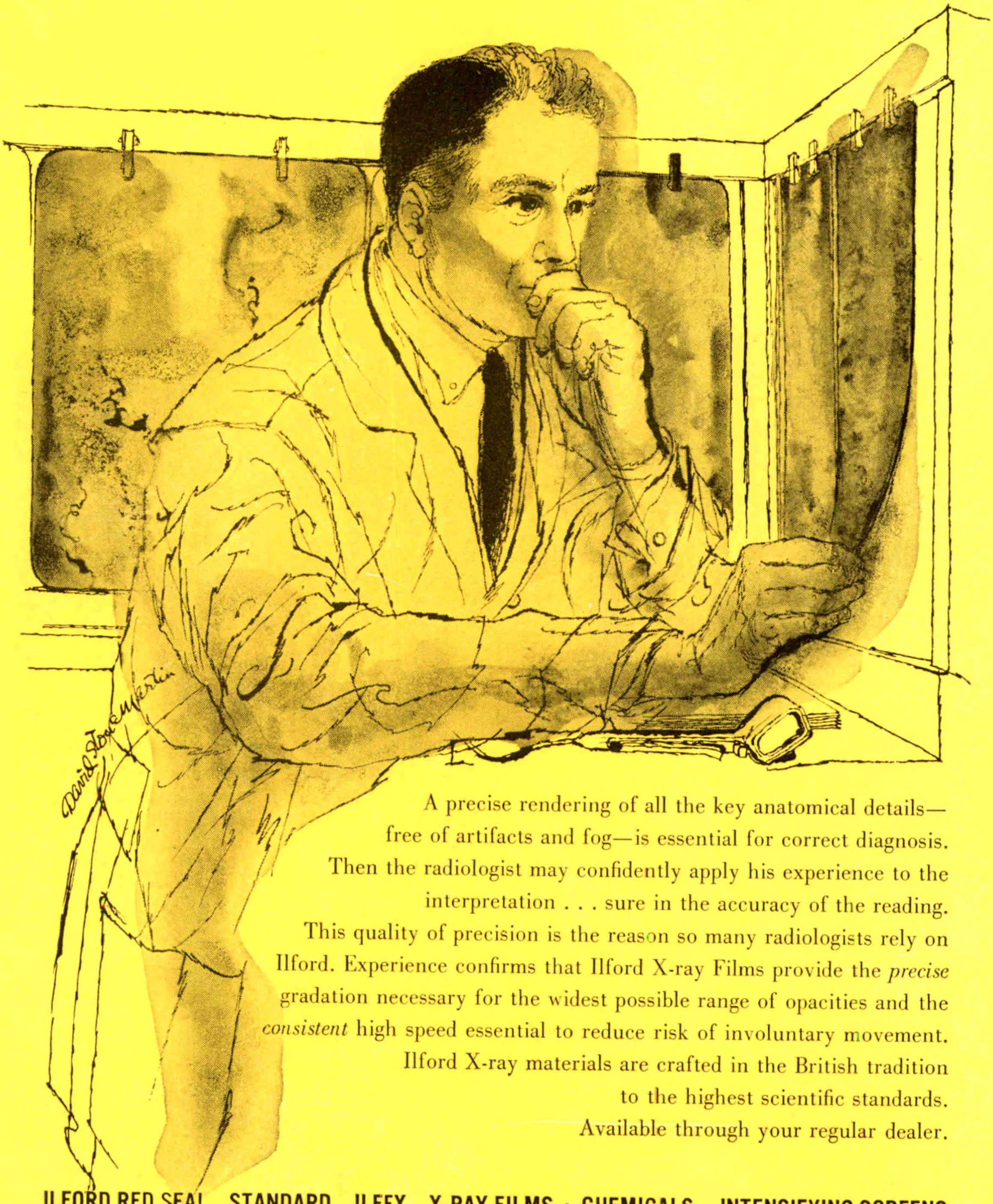

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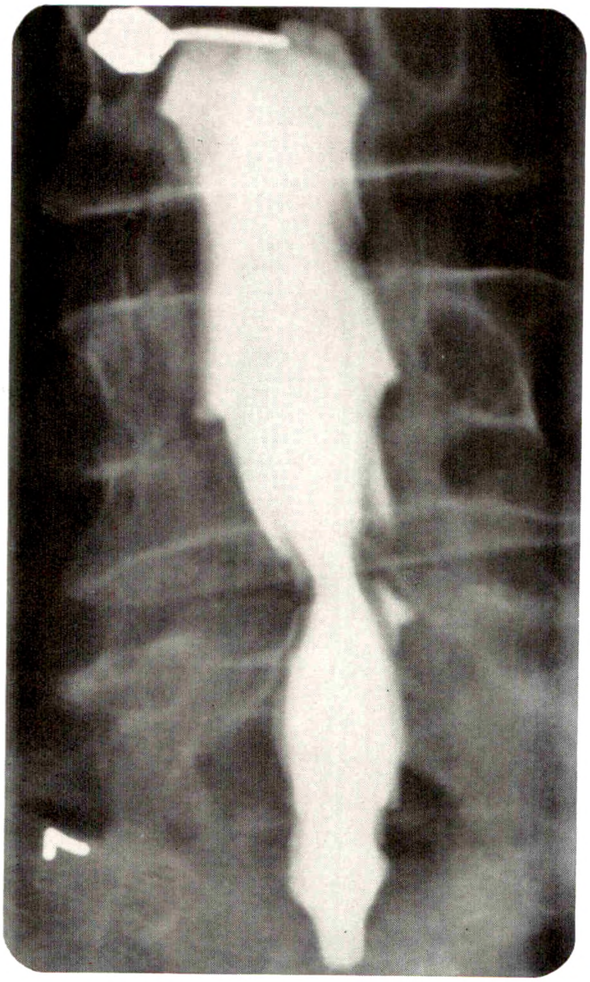

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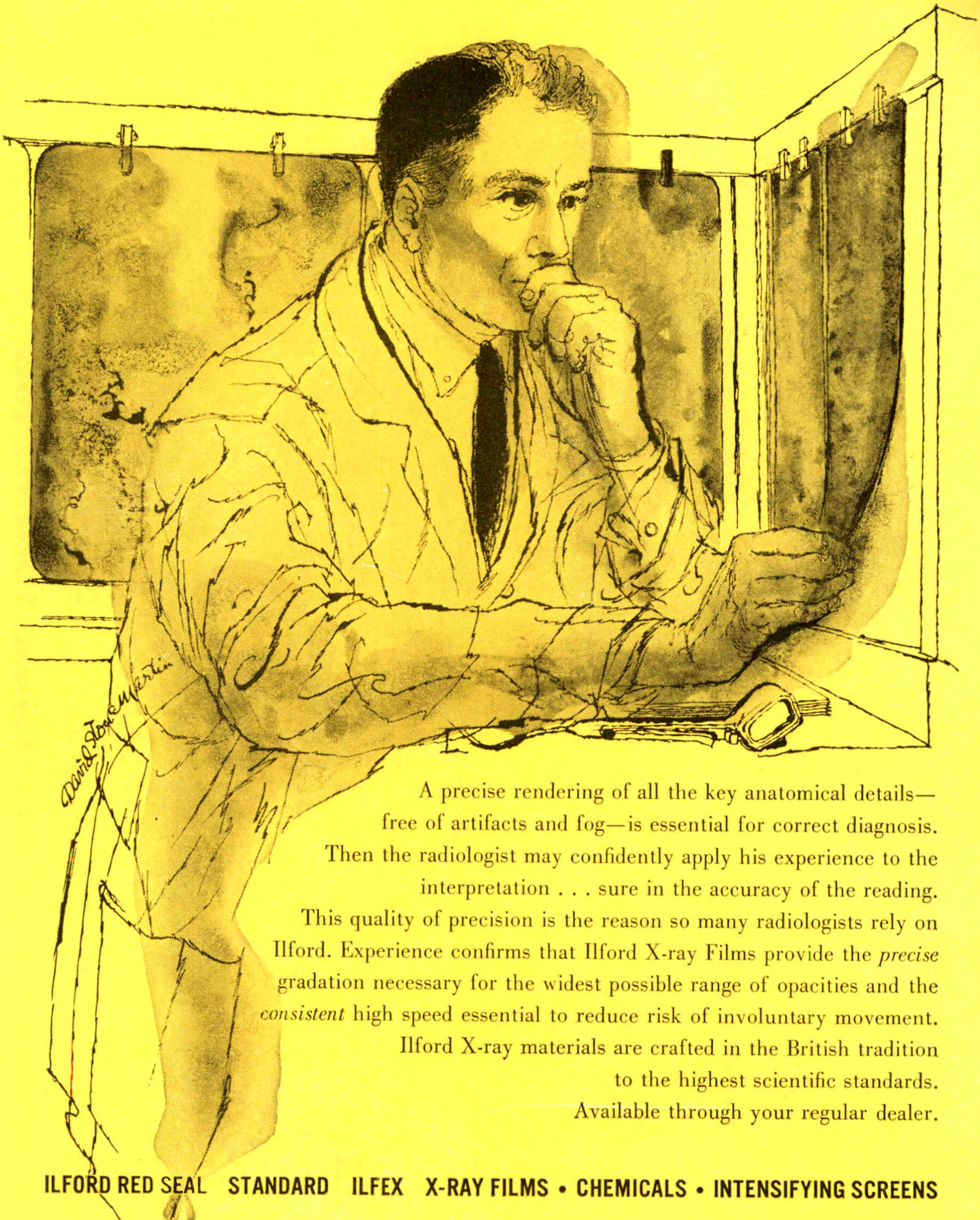

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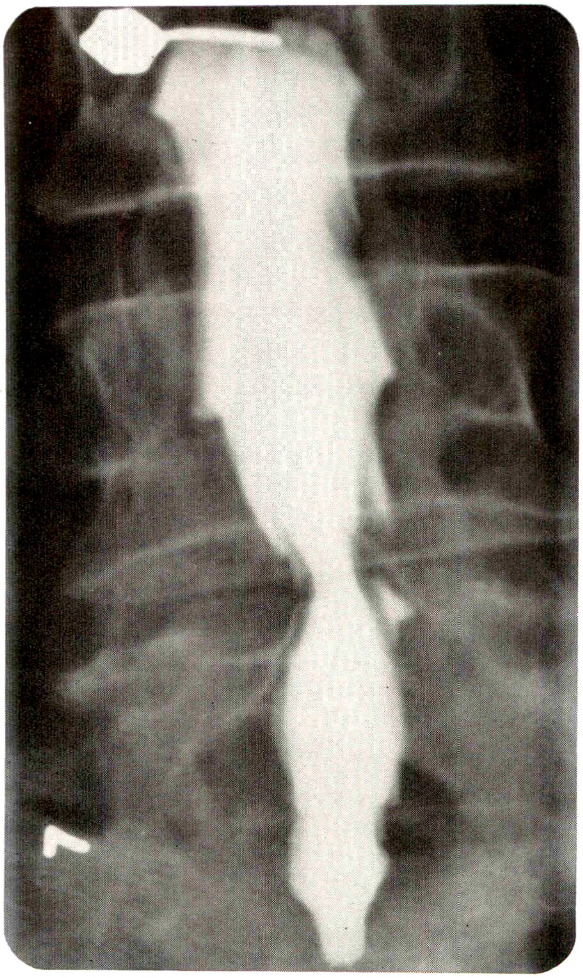

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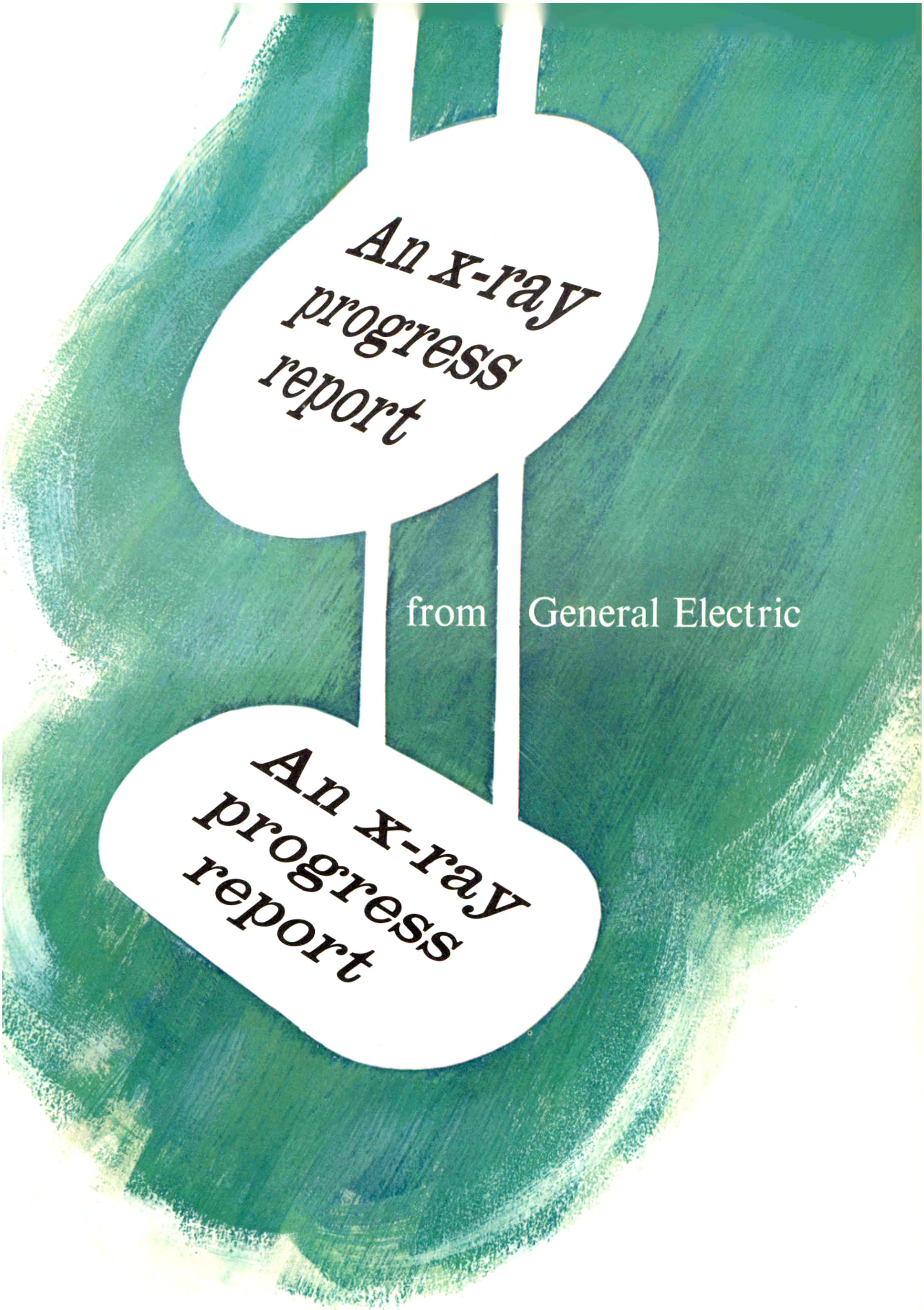

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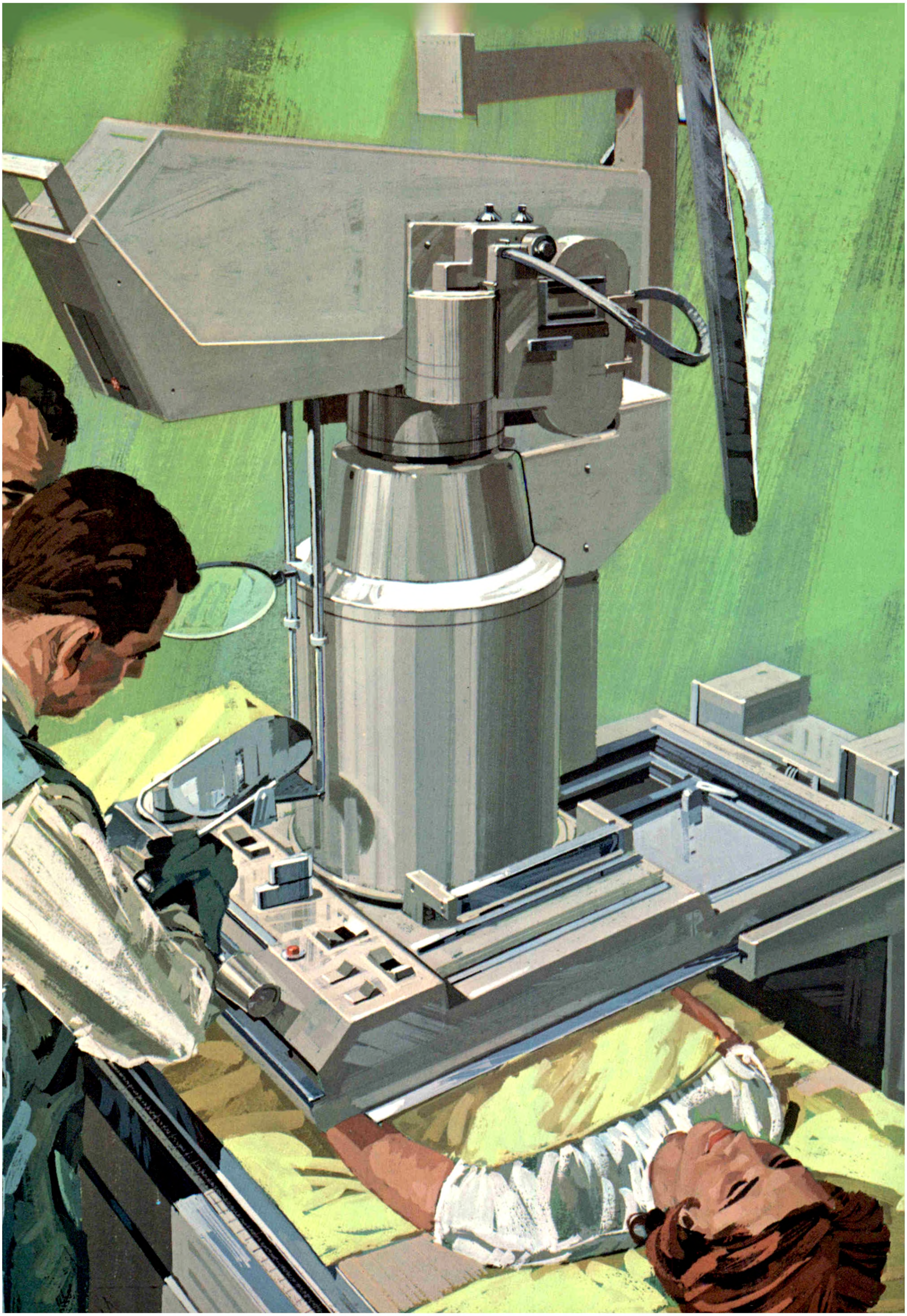

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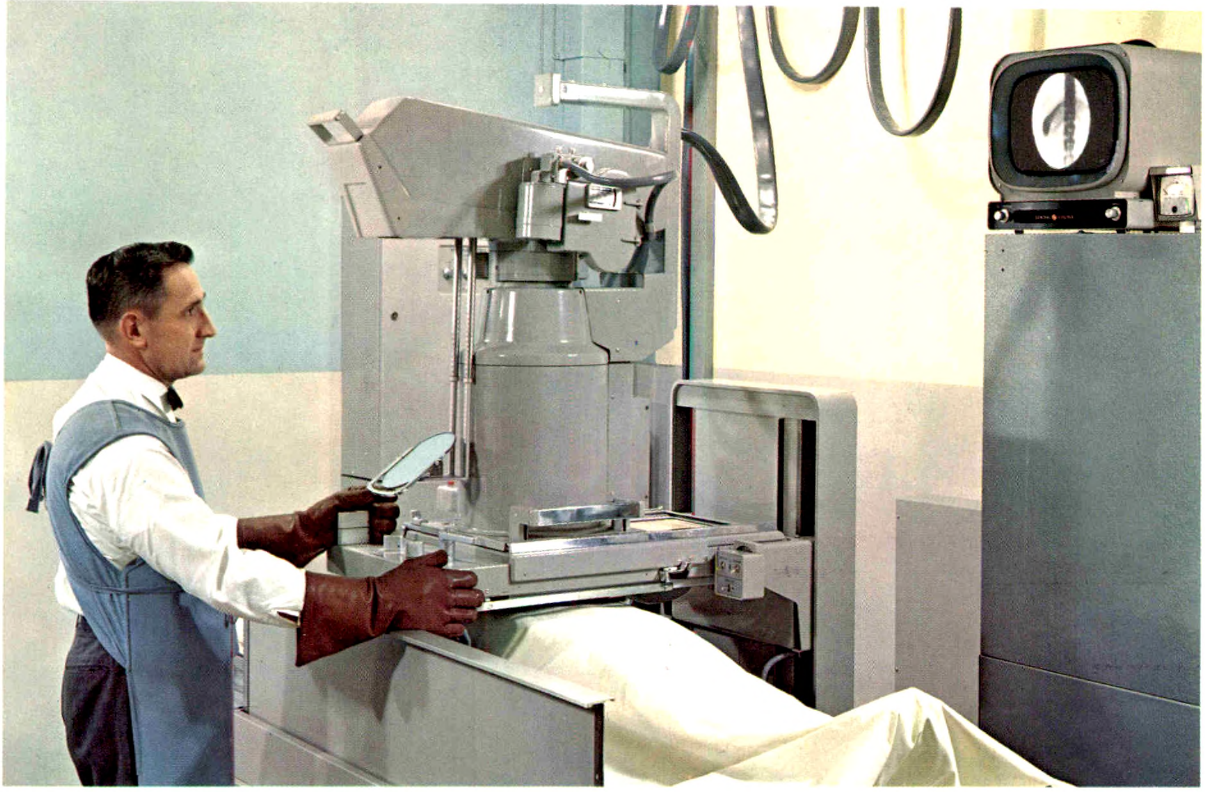

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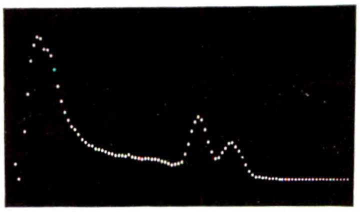

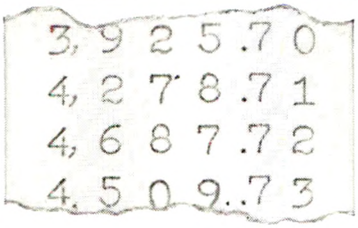

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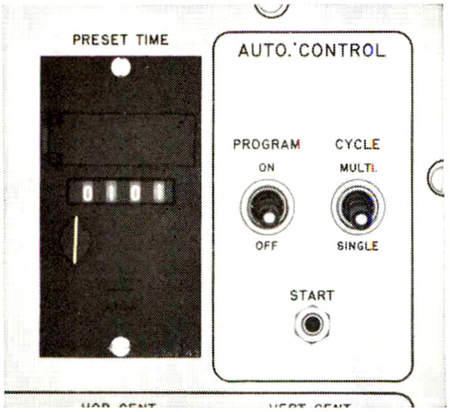

automatically — in a fraction of the time required by a scanning spectrometer

with the

GAMMASCOPE®

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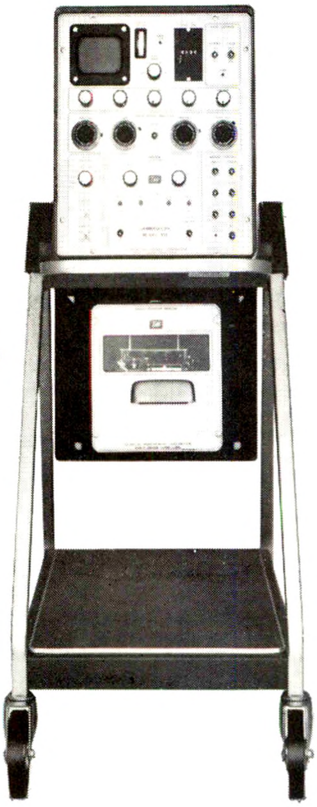
including digital printer



The Gammascope provides extremely fast and accurate analysis of whole body counts, thyroid uptake studies and virtually all other medical and biological applications of nuclear radiation. Yet the price of the Gammascope, including a digital printer, is comparable to that of most single-channel scanning spectrometers.

After initial set-up and calibration the Gammascope will automatically accumulate 100 channels of data — no manual or electrical scanners are needed. The entire analysis operation takes a small fraction of the time that would be required by a single-channel spectrometer.

The build-up of a radiation energy spectrum in the magnetic core memory may be observed on the built-in cathode ray tube display. After accumulation is complete, stored data is read out in digital form — far more accurately than an analog plot made with a strip chart recorder.

The Gammascope combines both single and multi-channel capabilities. A variable "window" (restricted energy range) permits selection of any area of the spectrum, for intensification and study. The primary energy peak can be isolated for count summation by an auxiliary scaler.

All the circuits including high voltage supply, linear amplifier, preset live timer, live time meter, add/subtract logic and static or dynamic display are built into the single, highly portable unit. This essentially replaces an entire rack of equipment that would make up a complete single-channel scanning spectrometer.

Complete operating data and applications information are available from local TMC offices or from Technical Measurement Corporation, 441 Washington Avenue, North Haven, Connecticut. 203 239-2501.

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a new aqueous bronchographic medium

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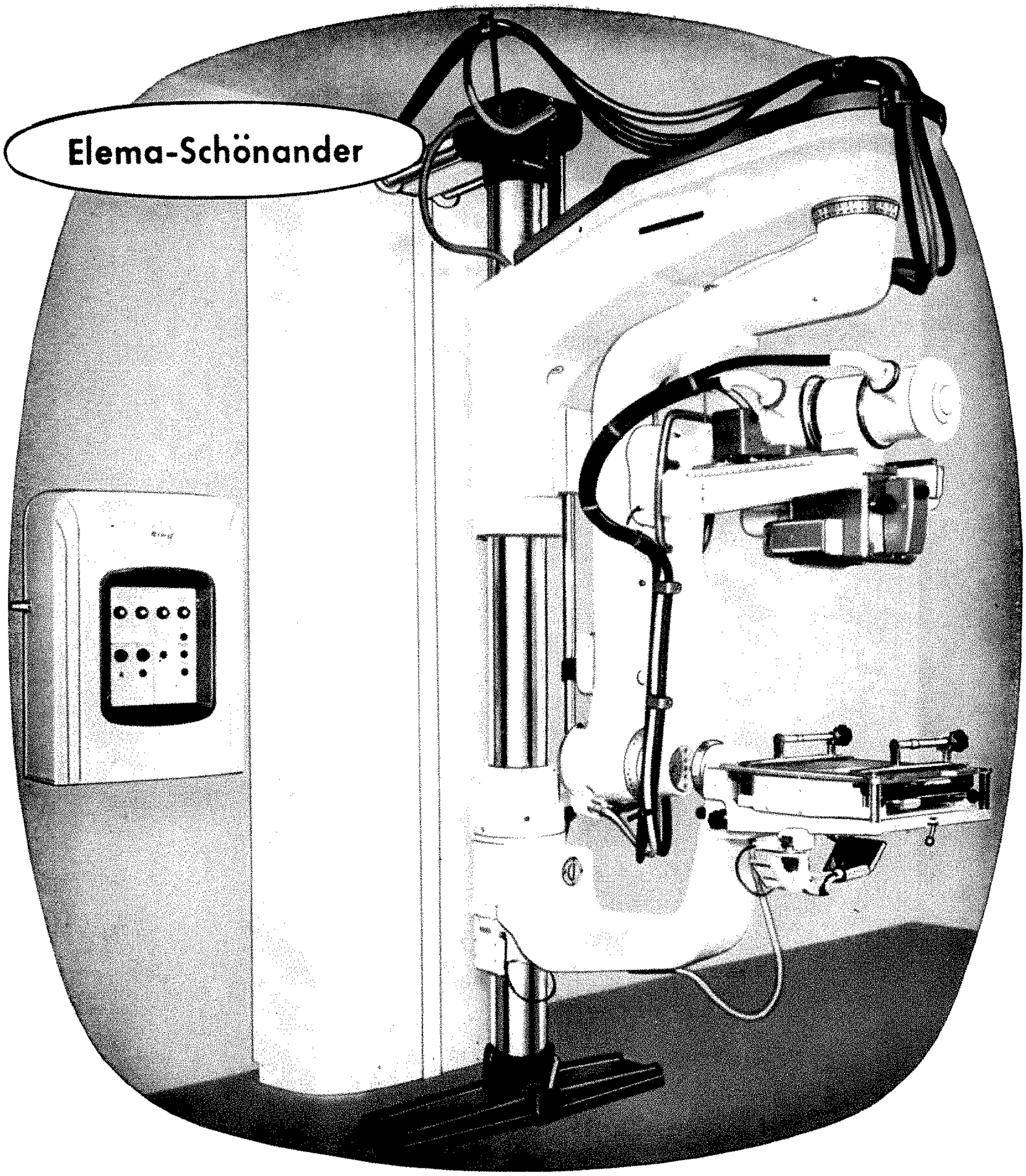
HYTRAST (iopydone, iopydol) gives an *interpretive* third dimension to bronchograms by combining higher radiopacity with a remarkably uniform adherence to mucosa. This double contrast effect—air plus medium—clearly traces the mucosa of every bronchial segment for more accurate and dependable diagnosis of bronchial lesions.

HYTRAST (iopydone, iopydol) is an aqueous suspension that offers an unusual degree of contrast by virtue of its high iodine content. In addition to providing sharper, clearer images of bronchial segments, it is miscible with bronchial secretions, yet its optimal viscosity gives the operator control of flow . . . so adherent to bronchial mucosa that coughing rarely produces alveolarization. Eliminated from the lungs by postural drainage and absorption; lung fields are normally clear to x-ray examination in 2 to 7 days.

HYTRAST (iopydone, iopydol) appears to be slightly more irritating to bronchial mucosa than oily media, but less so than other previously used aqueous preparations. A self-limiting temperature elevation may be noted particularly where alveolarization inadvertently ensues and elimination is delayed. The rare occurrence of mild bronchospasm, transient pneumonic infiltration, and atelectasis has been observed. Thyroid function tests, such as PBI determination or thyroid uptake studies, etc. should be carried out prior to the examination. Bronchography should be approached with caution in the markedly debilitated patient.

Similar to other bronchographic contrast media, bronchography with the use of HYTRAST (iopydone, iopydol) is contraindicated in: markedly diminished pulmonary function; heart failure; conditions associated with high fever; acute pneumonia; acute asthmatic attacks; rare existence of iodine sensitivity; massive pulmonary hemorrhage. Supplied in 25 ml. vials containing 20 ml. sterile aqueous suspension: 50% w/v of combined iodine as a mixture of N (2,3-propyldiol)—3,5 diiodopyridone—4 and 3,5 diiodopyridone—4. Consult the product brochure for complete information on administration.

FOUGERA



Mimer Universal X-Ray unit, designed for Neuroradiology and other special radiographic work.

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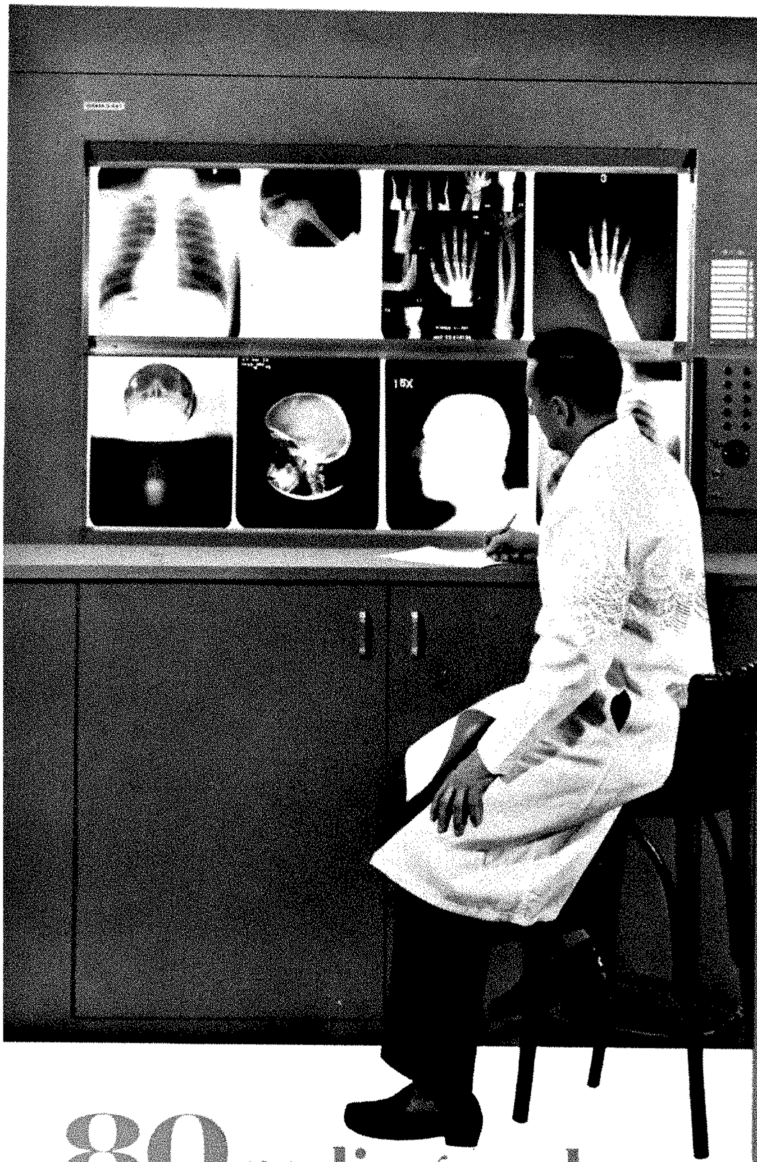
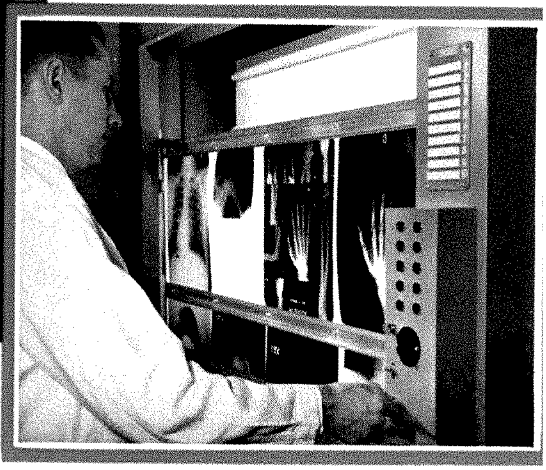


Film carriers are identified on a title-slip indexing rack. Key switch precludes unauthorized operation.



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Eminently practical way to view (and review) *droves* of radiographs in brisk, orderly fashion. Saves *time:* comes up with the wanted film (or series) in seconds. Saves *space:* offers viewing capacity equal to twenty banked four-film illuminators in only 16½ sq. ft. floor coverage.

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Ask your local Picker man for details, or write
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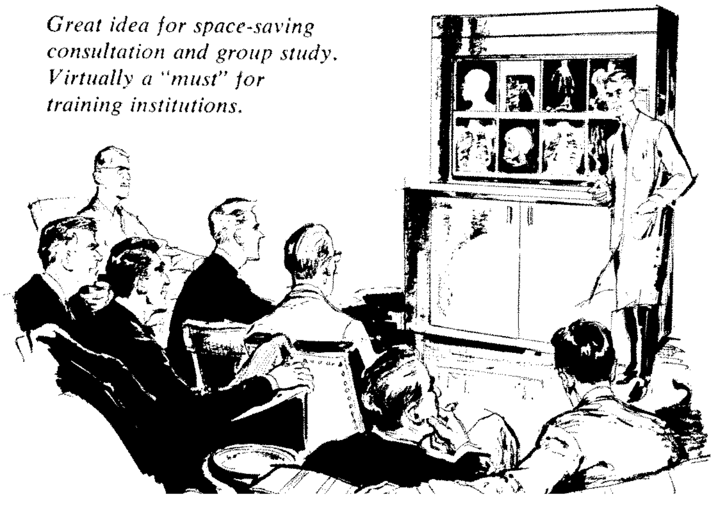
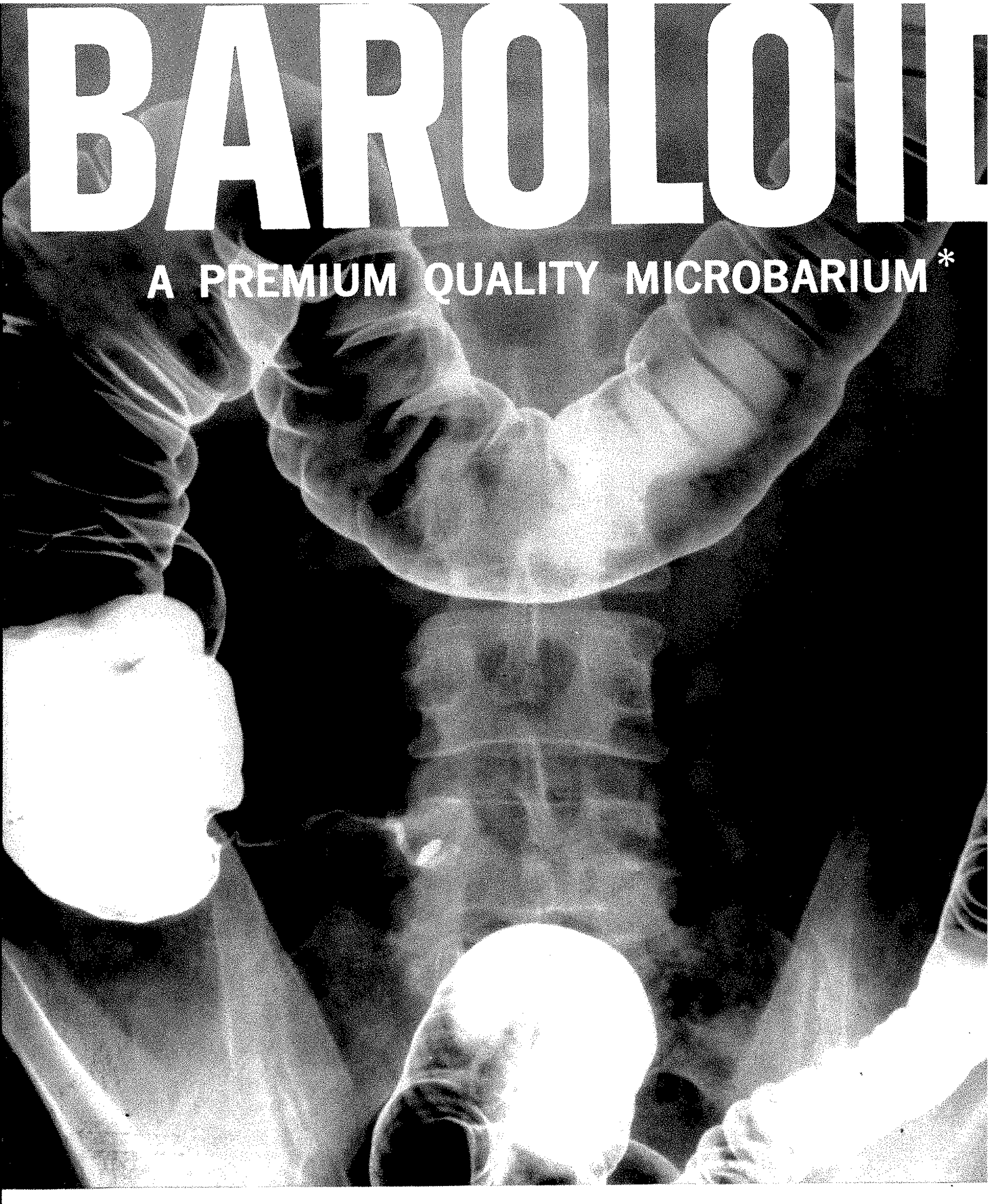
Great idea for space-saving consultation and group study. Virtually a "must" for training institutions.





the ideal product for air contrast colon studies, because . . .

Excellence of mucosal coating — continuous and non-segmenting. Non-flocculating, even on "post-evac." Coating does not tend to dry, crack or peel after repeated evacuations or prolonged examination. In 10, 50, 100 and 250 lb. containers.

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read it loud and clear-

CRONAR* polyester film base, available exclusively from Du Pont, has a unique optical clarity that lets more light through to give you sparkling images to read.

This polyester base is almost impervious to water and processing solutions. Films don't go limp in automatic processing units—they transport better with less chance of jamming.

CRONAR is chemically inert and free of radioactive contamination—significantly reducing the incidence of bothersome black spots.

And the exceptional strength of CRONAR permits a thinner base. This brings emulsion layers closer together, reduces parallax, gives you a sharper image.

You'll see (and feel and hear) the difference when you snap a CRONAR base film up on the viewbox.

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Proper density is guaranteed by the Amplimat, the automatic ionization-type

several selectable areas. To ensure positive positioning, the lightbeam indicator projects the location of the measuring areas on the patient. Just as in the case of the modern camera, automatic exposure with Amplima pays off in consistent production of opti-

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Sharpness is increased by the 'continuously falling tube-load principle', which permits shortest possible exposure time with maximum available tube loading. Optimum of the high load characteristic and small focal spot sizes of the Super Rotalix tube.

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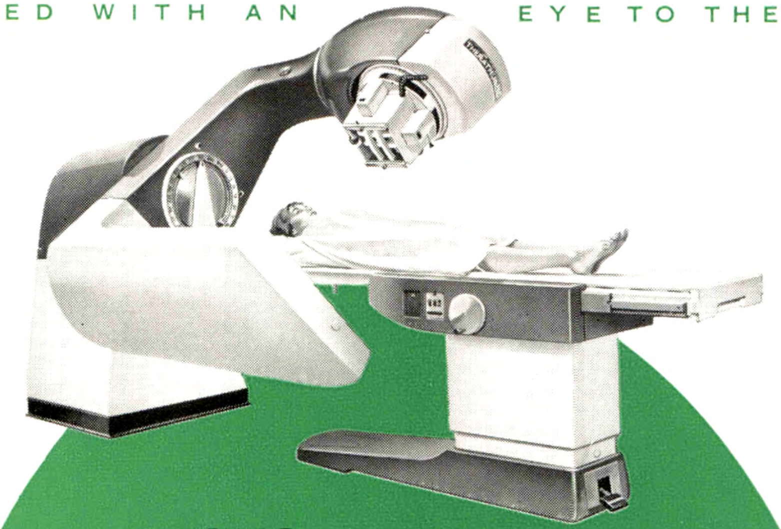
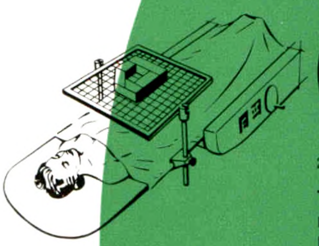
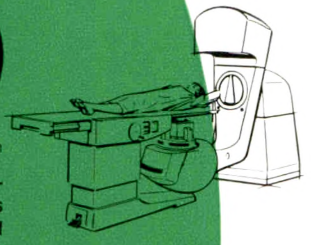


AECL'S

THERATRONS 60 and 80





206 R. per min. at axis of rotation

234 R. per min. at axis of rotation

The result of more than a decade of successful development and production, the new, widely accepted Theratrons by A.E.C.L. are designed to meet the flexibility demanded by modern therapy techniques. Special features include

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- **Accessories** — a selection of 15 standard, easily attached accessories for top precision in setup and treatment.
- **Isocentric Treatment Stretcher** — an integral unit component, featuring a choice of novel, highly functional top designs.
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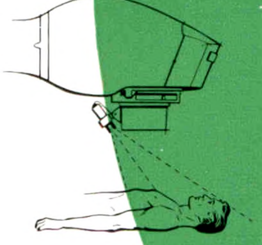
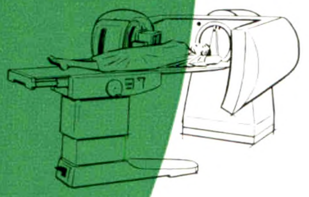
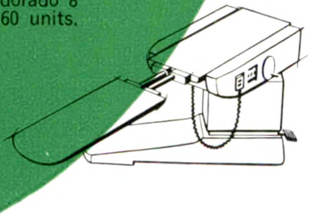




Our new brochure, BT-13 describes in detail the Theratron 60 and Theratron 80, also the Eldorado 6 and Eldorado 8 — AECL's new series of stationary beam Cobalt 60 units. Write for your copy today.



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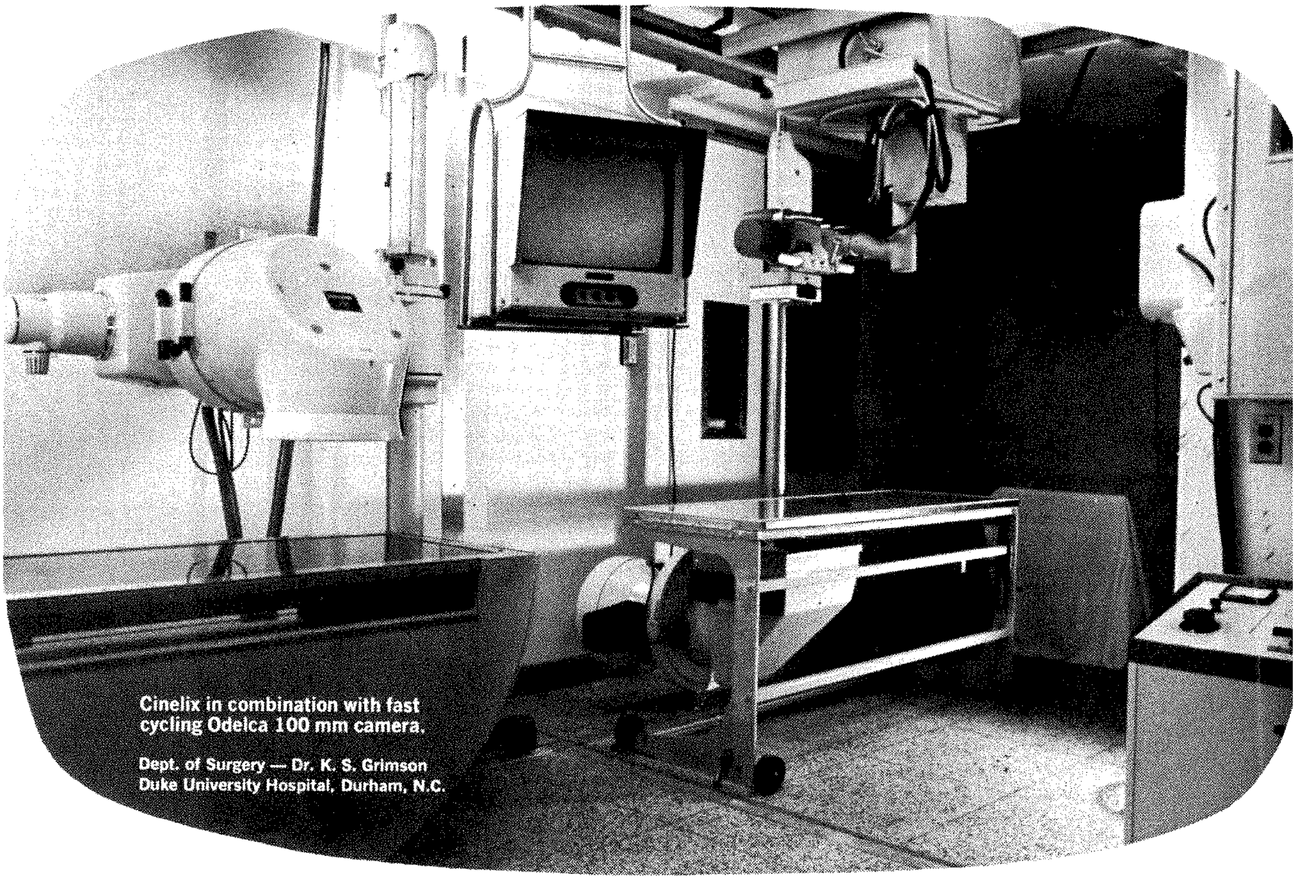

Cinelix in combination with fast cycling Odelca 100 mm camera.

Dept. of Surgery — Dr. K. S. Grimson
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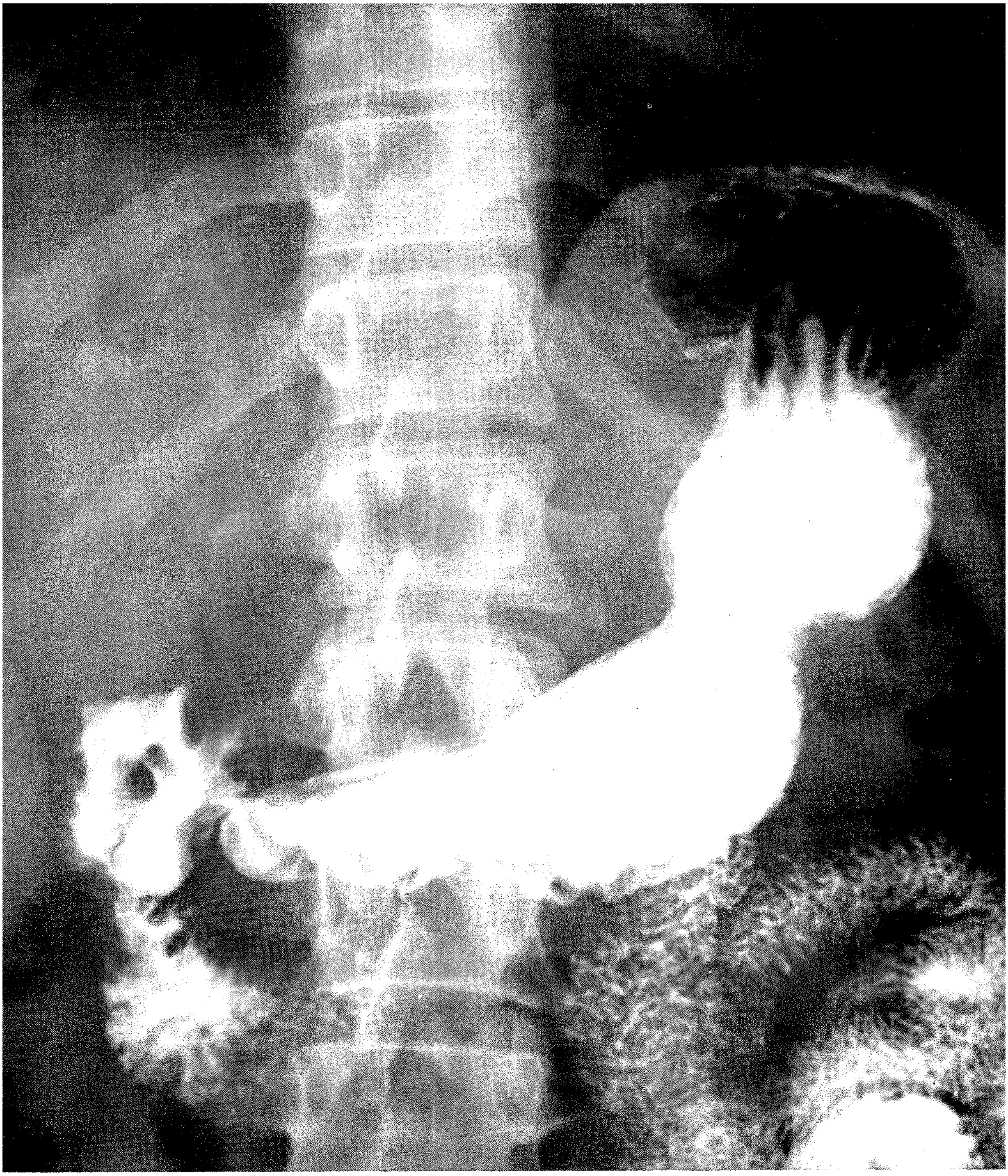

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■ Passes from the stomach to the duodenum in a smooth flow through the pyloric sphincter. The duodenal cap is completely delineated to illustrate

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TYPE N *for use with intensifying screens*
Speed: fast
Contrast: good
Grain: normal
Base: blue, safety

Type N film is faster than the most widely used medical X-ray film in the United States—and it costs less. This film is available with square corners in boxes of 25 or 75 interleaved sheets. For rounded corners, and extra savings on economical Ferrania prices, order Type N in bulk packages of 300-sheet interleaved, or 500-sheet non-interleaved films. Bulk-packed Type N film is specially designed for processing in all automatic developing units.

SIMPLEX *non-screen, for use with direct X-rays*
Speed: very fast
Contrast: good
Grain: fine
Base: blue, safety

No cassette is needed with Simplex film—each sheet is sealed in a lightproof exposure envelope for radiography of limbs and extremities. Convenient guide lines divide the upper surface of the envelope permitting accurate masking of the film into four separate exposure areas. 25 Simplex exposure envelopes are packaged per box.

GAMMA *for ultra fine tissue work*
Speed: slow
Contrast: extremely high
Grain: extremely fine
Base: blue, safety

This new Ferrania film brings unprecedented detail to mammography and other ultra-fine tissue radiography. Gamma film is compatible with all standard developing systems, and is packed 25 exposure envelopes per box.

IC2 *for very fine tissue work*
Speed: medium
Contrast: high
Grain: very fine
Base: blue, safety

IC2, slightly faster than Gamma film, permits additional savings for mammography and similar fine tissue work when the maximum requisites are high contrast and very fine grain. It is packed 25 exposure envelopes per box.

X2A and X3V *for photofluorography*
Speed: fast
Contrast: high
Grain: fine
Base: blue, safety

Ferrania films for photofluorography record all details of the smallest structures. X2A is highly sensitive to blue and violet light, and is used with blue fluorescing screens. X3V is orthochromatic, and is used with yellow-green fluorescing screens. Both films are available in 100- or 550-ft. rolls of 70mm-wide film, wound emulsion side in on cores.

DIRECT POSITIVE *for fast reproduction*
Speed: medium
Contrast: excellent
Grain: fine
Base: clear, safety

The special, clear safety base of this film permits an exceptional reproduction of any radiograph. None of the definition or contrast of the original will be lost. In fact, this film can actually be used to improve these factors. Direct positive film does not utilize intermediate copies and makes reproductions in as little as two minutes. It is packed in boxes of 25 interleaved sheets.

Seven *ferrania* X-ray films meet your needs for quality radiographs

Ferrania offers substantial savings on excellent medical X-ray films for all diagnostic applications. Name your requirement—screen or non-screen radiographs, fine tissue work, or photofluorography. Ferrania has six films of unmatched quality to fill these needs. The seventh, a high-contrast, direct positive film, reproduces even the finest details of a radiograph. Ferrania-formula chemicals, in addition, guarantee that the high contrast and clarity of Ferrania films will be retained during processing.

Every sheet and roll of film meets Ferrania's exacting standards of performance. This is true for the film you buy today, next month, or next year. Such consistency is the result of Ferrania's exacting quality control program—one that has supplied films of premium quality to the world for more than 35 years.

To find out more about Ferrania quality, test it. A request to Cenco X-Ray brings a test quantity of film (any of the seven types) and a catalog from your local Ferrania dealer. Also included: a copy of *Radiographica*, a technical journal of X-ray diagnosis published as a service by Ferrania.

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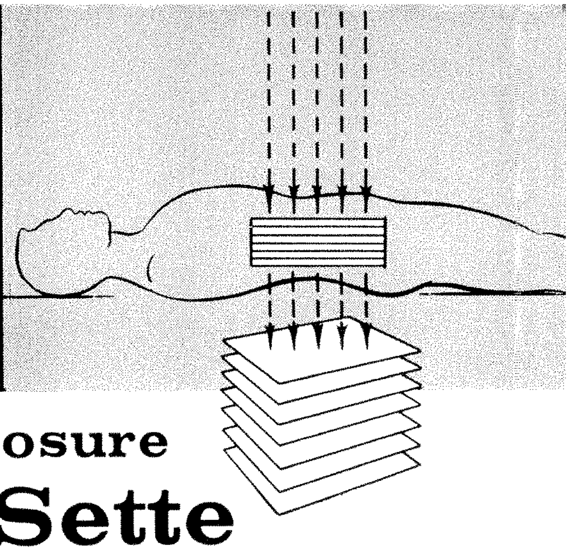
easier, faster body-section radiography — with reduced dosages

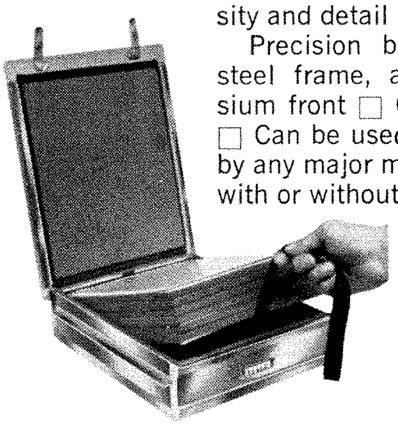


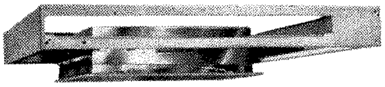
7 films at a single exposure

Halsey Multi-Sette

Can be installed in the Bucky housing without interfering with conventional Bucky use ☐ Provides 1-cm spacing between films — with comparable density and detail in all seven films.

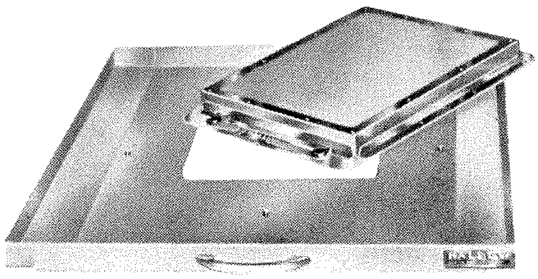
Precision built; polished stainless steel frame, aluminum door, magnesium front ☐ Opens and closes easily ☐ Can be used with x-ray tables made by any major manufacturer ☐ Available with or without screen book.





3 or 5 films at a single exposure

Halsey Multi-Sette Jr.



Similar to the 7-film Multi-Sette, but is designed to fit the conventional Bucky, using the special tray supplied.

The 5-film model has ½-cm spacing between films; the 3-film model, 1-cm spacing.

Available with or without screen book.

NEW-HALSEY PLESIOSETTE®

A new cassette for plesiosectional tomography. One exposure produces four films at approximately 1-mm level differences, through use of four pairs of matched screens with different speeds. Available in 8 x 10″ and 10 x 12″ sizes.

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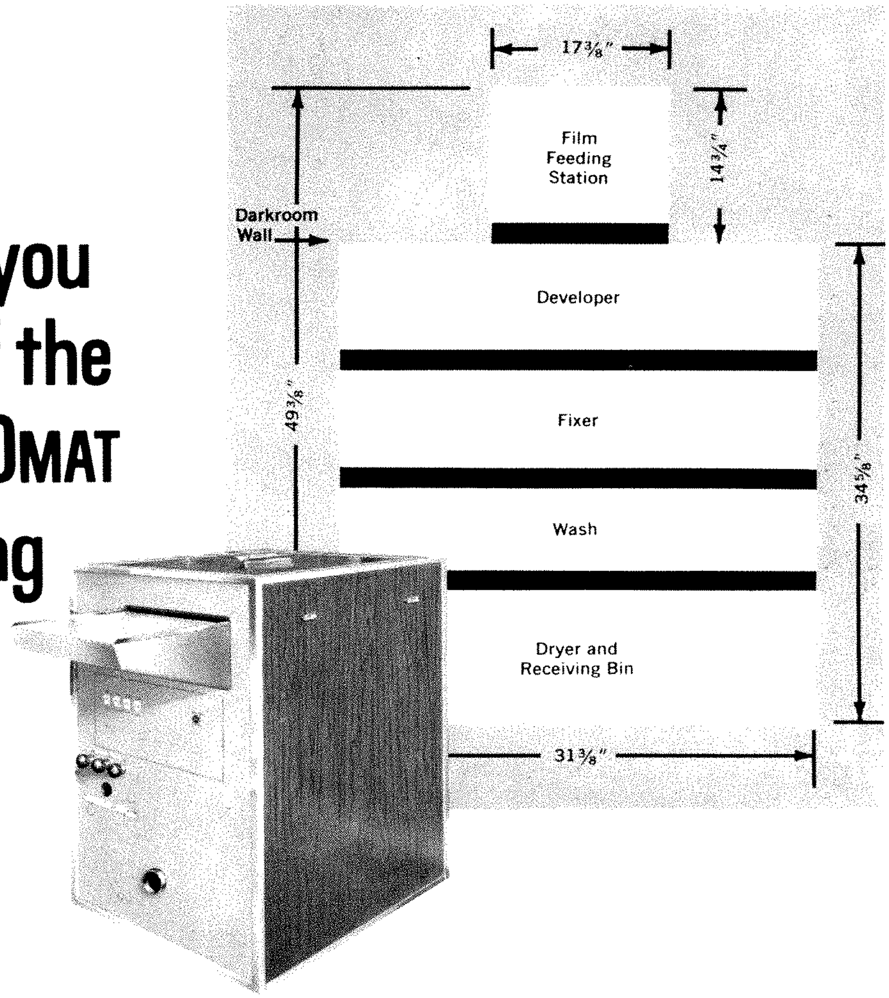
What do you expect of the KODAK X-OMAT Processing System?



Here's what it delivers—

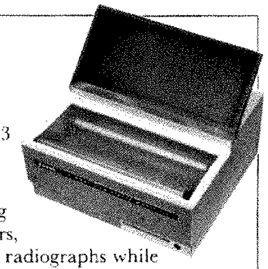
1. Reliable around-the-clock medical x-ray film processing that means
   - Improved service to referring physicians and patients
   - Smoother x-ray department operation
   - Increased efficiency in the department
   - Increased patient-load capacity
   - Fast service for any emergency
   - Film-processing capacity to meet expanding needs
   - Processing of uniformly excellent quality
2. Design that fits the requirements of radiological practice in private office, clinic or hospital as to
   - TIME—processing cycle, 7 minutes
   - SPACE—less than half the floor area of a hospital bed
   - CAPACITY—115 sheets of film per hour (intermixed sheet-film sizes)
3. Service at any time

   You can depend on your KODAK X-OMAT Processor dealer for installation, parts, and service because his men have been trained at the KODAK X-OMAT Center in Rochester, N. Y.

The KODAK X-OMAT Processing System is the result of Kodak's long and wide experience in film-making and film-processing chemistry, film-processing mechanics and film-drying procedure. It's an interesting fact that more than 400,000,000 radiographs have been processed by the KODAK X-OMAT Processing System.

NOW—AUTOMATIC FILM-FEEDING ACCESSORY

KODAK X-OMAT Film Feeder for Models M4A, M4, and M3 Processors available.



1. SAVES TIME—In offices or departments not needing full-time processor operators, technicians can be making radiographs while previously exposed films are being processed.
2. INCREASES EFFICIENCY—Full-time processor operators can handle other duties while films of several patients are being processed.

To get all the facts and details call a KODAK X-OMAT Processor dealer or write for brochure.

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During the year 1963, GASTROPAQUE® was administered to more than one and one-half million patients in the United States and foreign countries. This phenominal record has been the result of our efforts to keep the quality up and the price down; your continued assistance will be greatly appreciated.

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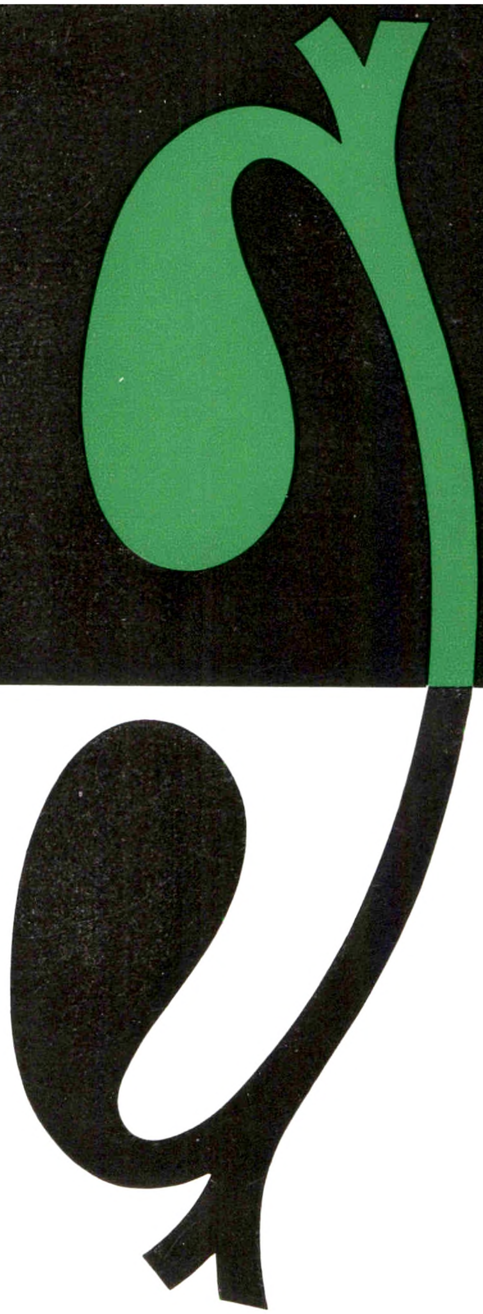
★ *X-Ray accessories for those who demand quality* ★



In cholecystography coming events will cast their shadows

The need for gallbladder surgery, for example. *Better contrast visualization*, of course means more *precise diagnosis* — the reason why well-tolerated Telepaque (brand of iopanoic acid) has so firmly established itself in oral cholecystography and cholangiography. Telepaque not only provides gallbladder shadows with better contrast, and improved visualization of the ducts, but it does so without disturbing gallbladder physiology. Convenient and economical, too.

Side effects, which are usually mild, include nausea, vomiting, diarrhea, dysuria. *Contraindications* are acute nephritis and uremia, and gastrointestinal disorders which prevent absorption of the medium.

Usual Dosage: 3 Gm. (6 tablets) at night after a light supper. Tablets of 500 mg., envelopes of 6 tablets, boxes of 5 and 25 envelopes; and bottles of 500.

ell-tolerated medium with distinctly better contrast **Telepaque**®

brand of **iopanoic acid**

Get wider latitude, better definition

with Ansco High-Speed film processed in Liquamat® Chemicals.

Remarkable radiographic detail and contrast — the two factors that mean most to you — have made High-Speed Film a "right hand" in radiology.

And if you process High-Speed Film in an automatic roller processor, new Liquamat® Chemicals bring a new degree of radiographic quality. Tests also show that no other chemicals for automatic processing equal Liquamat in the elimination of artifacts, sludging and staining.

Let your Ansco Man, an expert in the technical requirements of radiography give you a demonstration of these fine materials.

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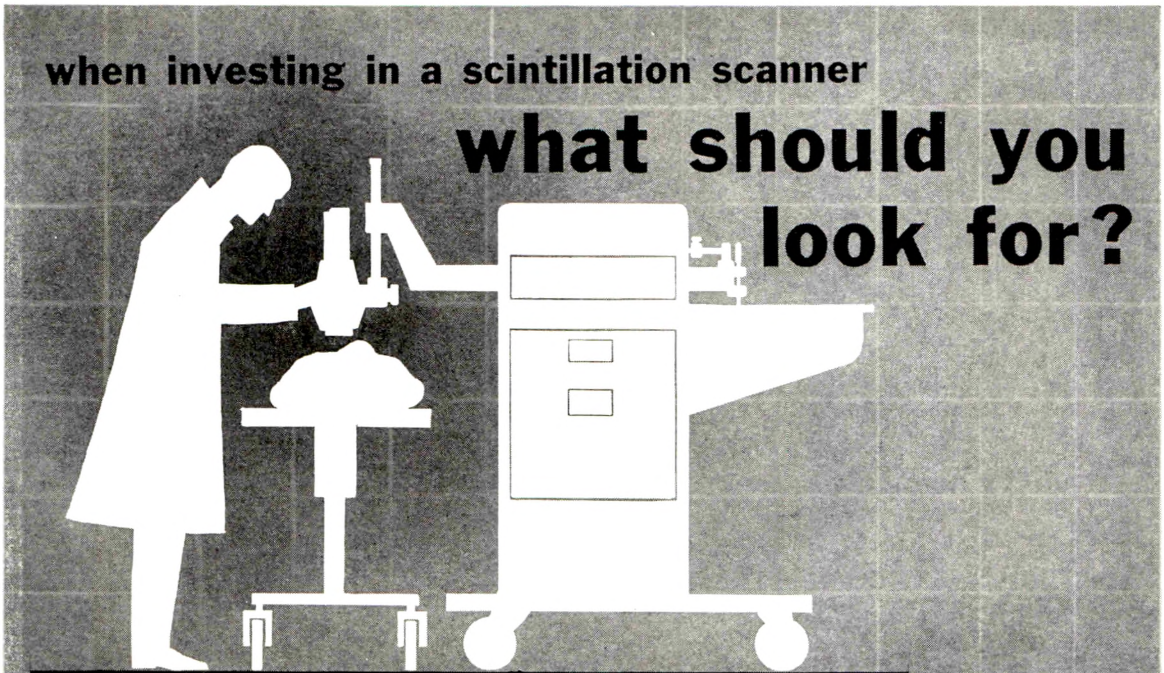
BINGHAMTON, NEW YORK

when investing in a scintillation scanner

what should you look for?



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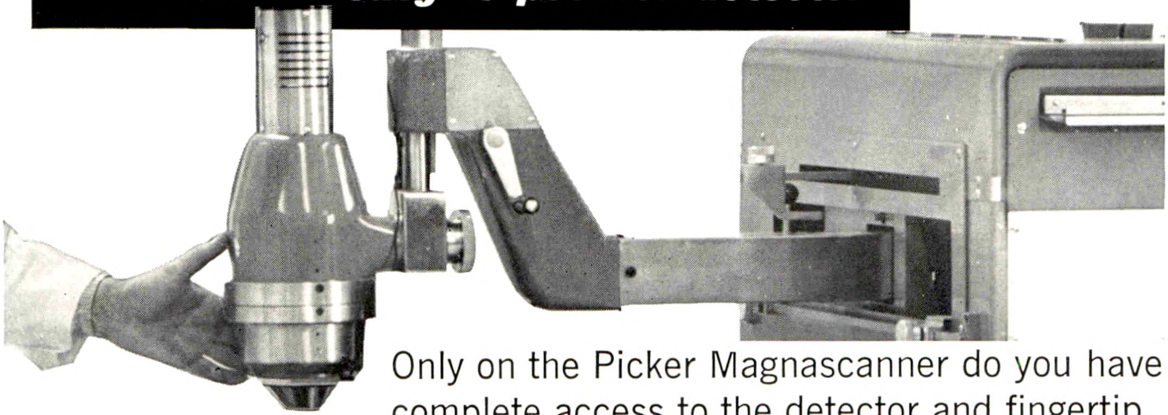

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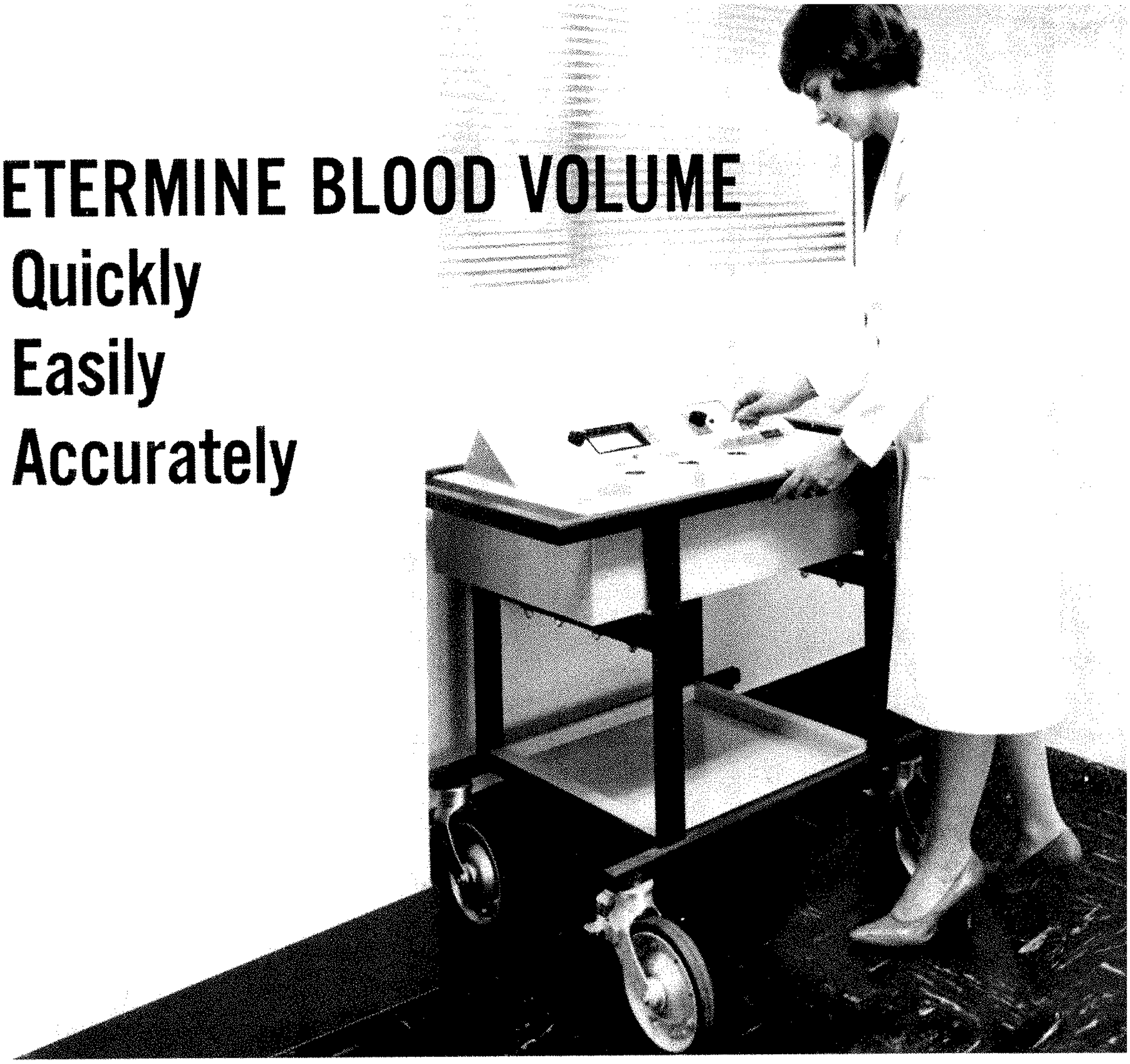

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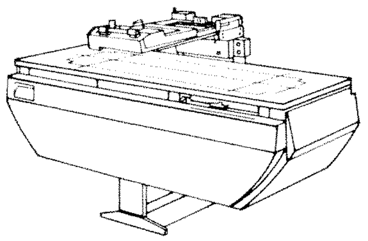

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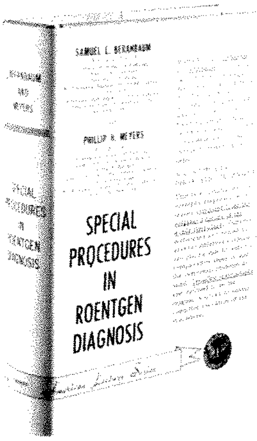

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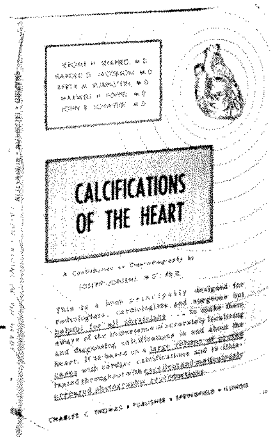

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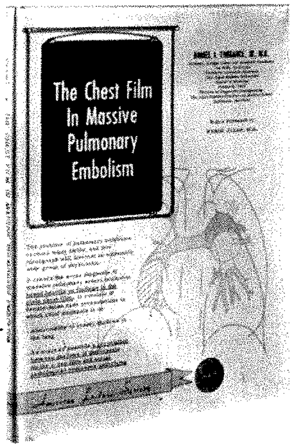

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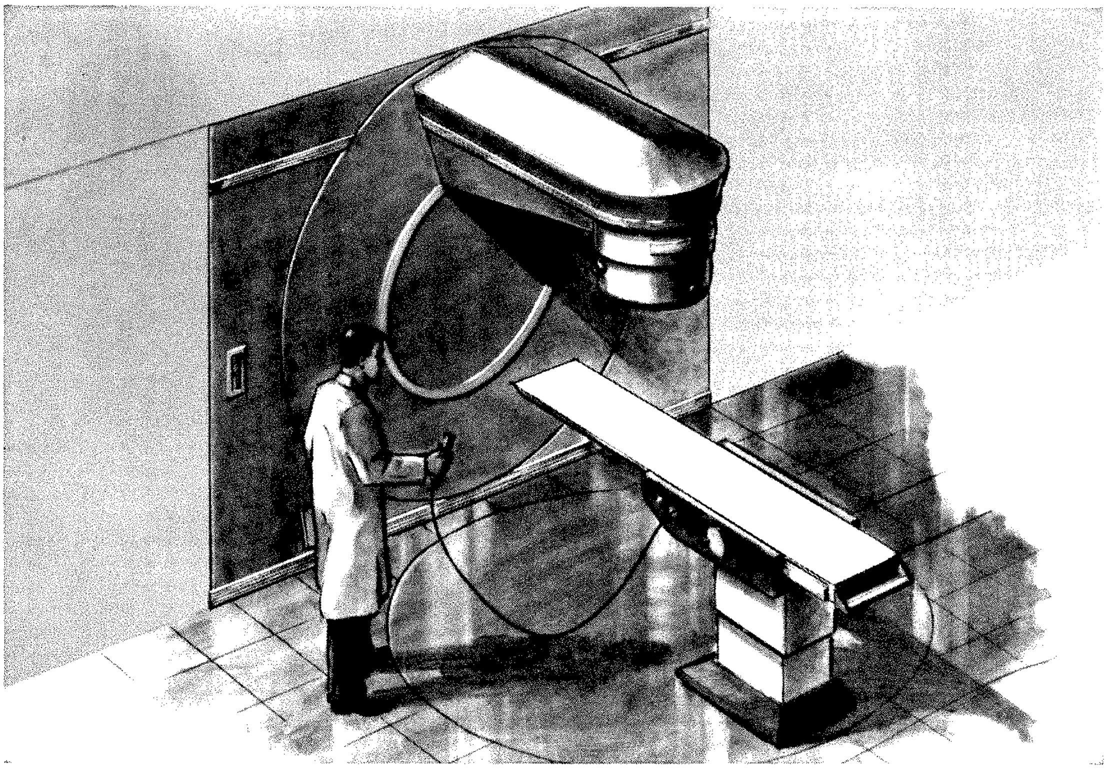

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CONGENITAL ABNORMALITIES OF THE PULMONARY ARTERIES*

By EDWARD B. SINGLETON, M.D., ROBERT D. LEACHMAN, M.D.,
and HARVEY S. ROSENBERG, M.D.
HOUSTON, TEXAS

IDENTIFICATION of both congenital and acquired abnormalities of the thoracic aorta has been possible for many years, even before aortography became a common procedure. With the advances in vascular surgery, it became necessary to demonstrate aortic lesions more accurately and this led to improved methods of opacifying the aorta and recording its image on roentgenographic film. Consequently, both congenital and acquired lesions of the aorta are now safely and accurately recognized, and their surgical correction is standard procedure in most institutions.

Abnormalities of the pulmonary artery and its branches are less well known, but in many instances are as important as those of the aorta. In those institutions where congenital heart diseases are investigated, anomalies of the pulmonary arteries are now recognized more frequently both by cardiac catheterization and by radiologic methods. Many of these defects are clinically significant and surgically correctable. Others are insignificant, but anatomically interesting, and others offer information regarding the physiology of the pulmonary circulation.

The following classification of pulmonary artery anomalies has been derived from cases seen at the Texas Children's Hospital during the past 8 years. This list excludes anomalies proximal to the pulmonary valve, *i.e.*, those complexes of transposition of the great vessels and anomalies of rotation of spiral septation of the truncus arteriosus.

I. Abnormalities of the undivided pulmonary artery
  1. Pulmonary valvular stenosis
  2. Supravalvular pulmonary artery stenosis
  3. Idiopathic dilatation of the pulmonary artery
  4. Pulmonary valvular insufficiency
  5. Coronary artery arising from pulmonary artery

II. Abnormalities of the pulmonary arteries
  1. Pulmonary artery atresia and hypoplasia

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* From the Departments of Radiology, Cardiology and Pathology, Texas Children's Hospital, Houston, Texas.

Presented at the Sixty-fourth Annual Meeting of the American Roentgen Ray Society, Montreal, Quebec, Canada, October 8-11, 1963.

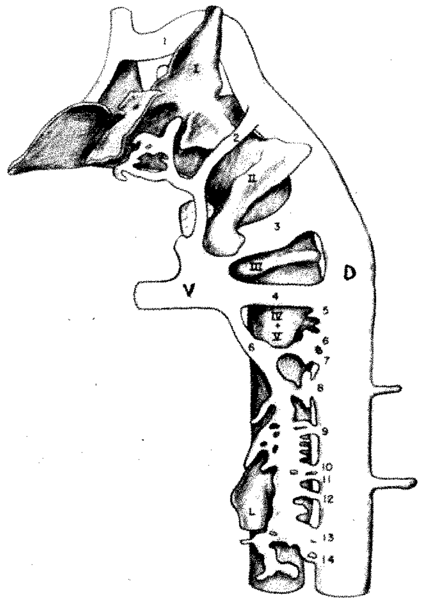

FIG. 1. Diagram of branchial arches of 12 day old embryo. Arabic numbers refer to the aortic arches and Roman numerals refer to branchial clefts. V–ventral aortic bud; D–dorsal aorta; L–lung bud; 4th aortic arch (left)-future aortic arch; 6th aortic arch–main pulmonary arteries.

  2. Pulmonary artery branch stenoses
  3. Retrotracheal left pulmonary artery
  4. Anomalous origin of the pulmonary arteries

III. Abnormalities of the pulmonary vascular bed
  1. Pulmonary arteriovenous fistula
  2. Pulmonary arterial sclerosis
    a. Medial hypertrophy
    b. Intimal sclerosis
    c. Arteritis
  3. Pulmonary telangiectasia

EMBRYOLOGY

An understanding of the embryology involved in the formation of the pulmonary vascular system is not only necessary for a complete evaluation of these abnormalities but also adds an enthusiastic appreciation of their recognition.

The definitive formation of the pulmonary arteries is accomplished through a series of events which seem to require more than the usual degree of embryologic complexity (Fig. 1). It is agreed that the proximal portions of the pulmonary arteries arise from the ventral portions of the sixth aortic arches, and the dorsal portion persists as the ductus arteriosus, most commonly on the left, but occasionally on the right or bilaterally. The sixth arch forms by the fusion of buds from each of the paired dorsal aortae with similar buds from the ventral aortic sac. According to Huntington,[10] the union is not end to end but end to side, leaving caudal outpouchings which ultimately become the pulmonary branches. At the same time, the lung bud develops as a ventral outpouching of the foregut and carries with it, from the paired dorsal aortae, a vascular plexus which Huntington called the postbranchial pulmonary plexus. Huntington described the complete formation of the sixth arch prior to its union with the postbranchial plexus. Bremer[2] indicates that the pulmonary arterial branches arise first as a capillary network, with the main channels defined at a later time. According to Coulter,[4] the main pulmonary arteries develop from the middle of the completed sixth arch. Coulter and Huntington both indicate that the ventral buds of the sixth arch originate either very near the origin of the fourth arch from the ventral aortic sac, or from the fourth arch itself.

From these considerations and an examination of Figure 1 (a reconstruction of the primitive arch system), one can readily see that it is almost miraculous that the pulmonary arteries develop with uniformity. It is easy to speculate that branch atresia of the main pulmonary arteries could result from a rudimentary bud from the sixth aortic arch. Multiple peripheral pulmonary artery branch stenoses would have to be explained as a failure of normal channel development in the postbranchial plexus. Bronchial arteries develop from the dorsal aortae and the postbranchial plexus and may exist as normal channels or as large collateral vessels or be the only blood supply

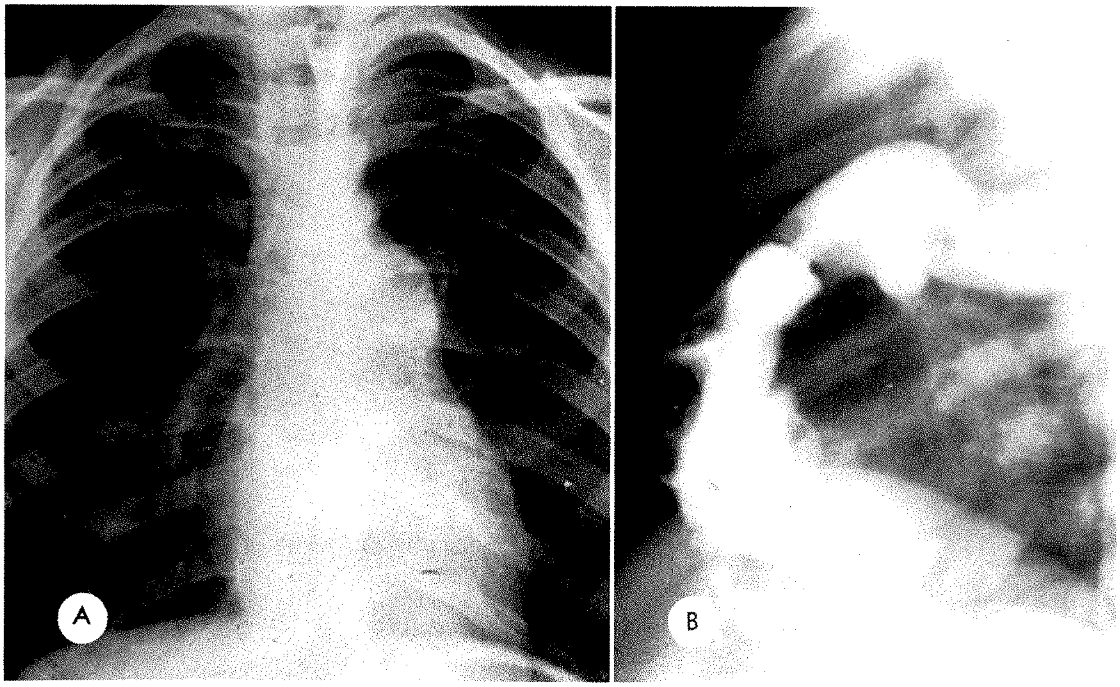

Fig. 2. Pulmonary valvular stenosis in a 7 year old boy. (*A*) Posteroanterior chest roentgenogram shows heart of normal size with dilated pulmonary artery segment. (*B*) Lateral angiocardiogram shows convex stenotic pulmonary valve with jet of contrast material distal to the valve.

to the lung. The pulmonary arteries will have an ectopic origin if the sixth arch buds fail to fuse or if the ventral segment atrophies and the pulmonary buds remain connected to the dorsal segment. In these cases the pulmonary arteries are usually long and arise from either the aortic arch or from the subclavian artery due to the proximity of the origin of the dorsal bud of the sixth arch to those of the fourth arch. This type of pulmonary arterial arrangement may be unilateral with a normal pulmonary artery supplying the contralateral side or bilateral in an unusual form of pseudotruncus arteriosus. In the following discussion of pulmonary artery abnormalities, reference should be made to the embryonic development described above.

I. ABNORMALITIES OF THE UNDIVIDED PULMONARY ARTERY

PULMONARY VALVULAR STENOSIS

Pulmonary valvular stenosis with an intact ventricular septum is a common form of congenital heart disease characterized by fusion of the pulmonary valve leaflets with resulting stenosis. Patients with this malady may be asymptomatic or may have varying degrees of exercise intolerance depending upon the severity of the stenosis. Cardiac catheterization demonstrates the increased right ventricular pressure with a normal or reduced pulmonary arterial pressure. The severity of the stenosis is proportional to the systolic pressure gradient existing between the right ventricle and the pulmonary artery.

The characteristic roentgenographic findings are a prominent undivided pulmonary artery segment, the result of poststenotic dilatation, and an over-all heart size which is essentially normal (Fig. 2, *A* and *B*). The pulmonary vascularity is usually normal although may occasionally appear diminished, especially if there is an associated atrial septal defect. Angiocardiograms will demonstrate the stenotic pulmonary valve, which characteristically shows a persistent distal convexity, as well as a jet of contrast material passing into the poststenotic di-

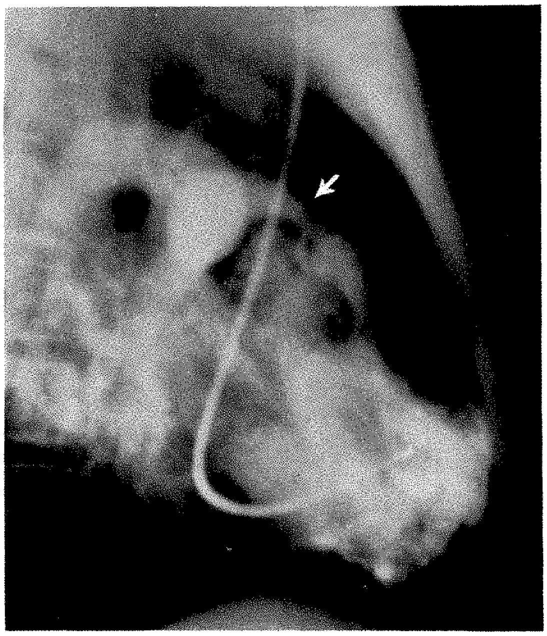

FIG. 3. Supravalvular pulmonary artery stenosis in a 2 year old boy. Lateral angiocardiogram shows supravalvular stenosis (arrow), as well as valvular stenosis.

lated segment. The width of the jet of contrast material entering the pulmonary artery is an index of the size of the valve orifice.

Idiopathic dilatation of the pulmonary artery and corrected transposition of the great vessels, in which the ascending limb of the aorta occupies the region normally formed by the pulmonary artery, may be confused with the roentgenographic features of pulmonary valvular stenosis, but clinical data, cardiac catheterization findings and angiocardiographic evidence will serve to differentiate these conditions.

SUPRAVALVULAR PULMONARY ARTERY STENOSIS

A few patients with stenosis of the main trunk of the pulmonary artery have been described, but isolated coarctation of the undivided portion of the pulmonary artery is extremely rare and when encountered may be associated with pulmonary valvular stenosis.[1,16] Since the sixth aortic arch does not contribute to the undivided or most proximal portion of the pulmonary artery, stenosis of the supravalvular type must be due to anomalous septation of the truncus arteriosus near the point of origin of the sixth aortic arch in the region of the ventral aortic sac. The combination of supravalvular stenosis with associated congenital peripheral stenoses of the pulmonary arteries is more common than supravalvular stenosis alone, and has been described by Kjellberg *et al.*,[11] and Gyllenswärd and his co-workers.[9] If the pulmonary artery constriction is severe, clinical and physical findings similar to pulmonary valvular stenosis will be present. In milder forms the condition is asymptomatic and identified only if cardiac catheterization and angiocardiography are performed for the investigation of a murmur.

The roentgenographic findings may be within normal limits and pulmonary vascularity is usually also normal. Only by angiocardiography can the stenotic pulmonary artery be identified (Fig. 3).

IDIOPATHIC DILATATION OF THE PULMONARY ARTERY

Idiopathic dilatation of the pulmonary artery is a benign abnormality in which cardiac function is unimpaired.[5] A pulmonary systolic ejection murmur is usually present, often accompanied by an ejection click, and is the usual reason for cardiac evaluation in these patients. The electrocardiogram is usually normal although frequently right bundle branch block is present. The right ventricular pressure is found to be normal and there is a slight decrease in the systolic pressure as the catheter enters the dilated pulmonary artery segment.

Roentgenographic examination of the heart shows the over-all heart size to be within normal limits and the pulmonary vascular shadows also appear normal (Fig. 4, *A* and *B*). The pulmonary artery may be markedly convex but the degree of prominence is not strikingly abnormal in many individuals. This abnormality is rarely encountered prior to 4 years of age and its etiology remains enigmatic. It is possible that this represents a congenital malformation of the structure of the pulmonary arterial wall; however, microscopic examination of sections taken from such deformed vessels shows normal elastic tissue and no evidence of cystic necrosis except in those few cases associated with Marfan's syndrome. It is also possible that these dilated vessels could result from hemodynamic factors. The age distribution would suggest that it is an acquired disorder.

PULMONARY VALVULAR INSUFFICIENCY

Marked dilatation of the pulmonary artery and its primary branches may occur in pulmonary valvular insufficiency with associated ventricular septal defect and overriding of the aortic root. These hearts are anatomically similar to cases of tetralogy of Fallot except for the presence of insufficiency of the pulmonary valve in addition to stenosis.[13] The valve ring is usually quite small and there is infundibular stenosis frequently. The heart is slightly enlarged and the pulmonary artery segment is prominent. The right and left branches are also dilated but the lobar and segmental branches appear diminutive, especially on angiocardiograms (Fig. 5). The over-all appearance is highly suggestive of pulmonary hypertension with secondary dilatation of the pulmonary artery, but there is no significant elevation of the pulmonary artery pressure. Presumably, the dilatation of the pulmonary artery and its major branches in cases of pulmonary valvular insufficiency is the result of the large stroke volume. The clinical findings are quite similar to those in Fallot's tetralogy: cyanosis, squatting, dyspnea, electrocardiographic findings of right ventricular hypertrophy, and a systolic ejection murmur at the pulmonary auscultatory area. There is in addition, however, a prominent early diastolic murmur of the semilunar valvular insufficiency type.

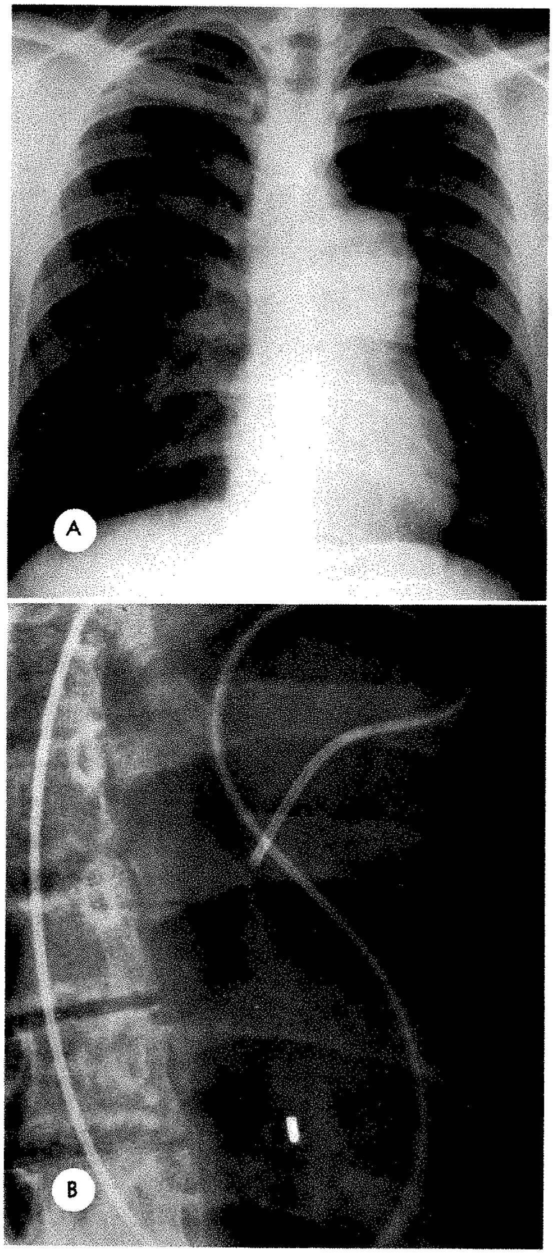

Fig. 4. Idiopathic dilatation of the pulmonary artery in a 15 year old girl. (*A*) Posteroanterior chest roentgenogram shows marked dilatation of the undivided pulmonary artery segment. (*B*) Spot roentgenogram shows end of catheter coiled within the dilated pulmonary artery.

ANOMALOUS ORIGIN OF THE CORONARY ARTERY FROM THE PULMONARY ARTERY

Although the left or right coronary artery or both may arise anomalously from the pulmonary artery, the anomalous origin of the left coronary artery is much more common than the right. This condition is being recognized with increased frequency during life and should be suspected in the infant who shows evidence of myocardial infarction. The initial clinical findings of these patients are most often irritability,

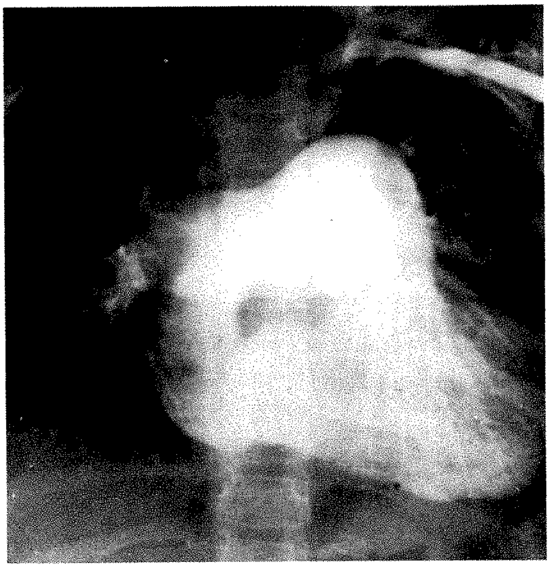

FIG. 5. Pulmonary valvular insufficiency in a 6 year old girl. Angiocardiogram shows marked dilatation of the right and left pulmonary artery branches with abrupt tapering of the lobar branches.

sweating, pallor and occasionally cyanosis. Presumably the irritability and apparent discomfort are manifestations of angina pectoris. Congestive heart failure ultimately develops and is frequently associated with respiratory infection. Approximately two-thirds of the patients with an anomalous coronary artery arising from the pulmonary artery die during the first year of life. Of those who survive, some are unaffected while others die from coronary insufficiency early in adult life. The myocardial ischemia has been explained by the low oxygen content of the venous blood from the pulmonary artery and the resulting low perfusion pressure of the anomalous coronary arterioles. However, a more acceptable theory proposes that an arteriovenous shunt is established between the two coronary arteries with the resulting passage of the arterial blood from the aorta-fed coronary artery to the myocardium and returning to the pulmonary artery by the anomalous coronary vessel. Perfusion studies performed during postmorten examination suggest that the passage of blood is from the myocardium into the anomalous coronary artery with drainage into the pulmonary artery. Consequently, the direction of blood flow in these cases is from the myocardium through the left coronary artery into the pulmonary artery.[15] Surgical ligation has been proposed as the treatment of choice consequent to these studies.

The coronary arteries arise as small endothelial buds from the dorsal aorta and rapidly grow over the myocardium. According to Grant,[8] they develop on either side of the dorsal aortic endocardial cushion at about the same time the septum of the truncus arteriosus is forming. The truncoconal ridge which separates the aorta and pulmonary artery normally forms anterior to the coronary buds. If the coronary arterial buds arise more anteriorly or if septation is displaced more posteriorly, one or both coronary vessels arise from the pulmonary artery.

Chest roentgenography as a rule shows cardiac enlargement, the left ventricle being the predominant chamber. The left atrium is also frequently dilated and the over-all roentgenographic appearance is very similar to that seen in infants with aortic stenosis or endocardial fibroelastosis, and, in fact, endocardial thickening and distortion of the mitral valve are commonly associated findings. Retrograde aortog-

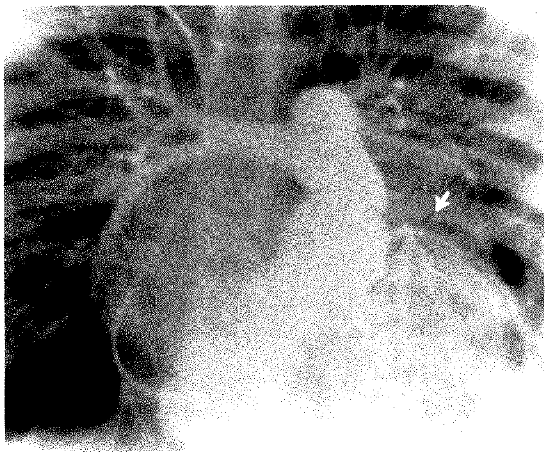

FIG. 6. Ectopic coronary artery in a 6 year old boy. Cineangiocardiogram shows the left coronary artery arising from the pulmonary artery (arrow).

raphy will reveal the absence of the normal left coronary artery which may be opacified by selective injection into the pulmonary artery (Fig. 6).

II. ABNORMALITIES OF THE PULMONARY ARTERIES

APLASIA AND HYPOPLASIA OF ONE PULMONARY ARTERY

The identification of a hypoplastic or aplastic pulmonary artery is usually made at the time of investigation of suspected hypoplasia of the lung. The patients are frequently asymptomatic although exertional dyspnea may be present. Unilateral absence of a pulmonary artery may occur as an isolated defect or in combination with other cardiac or vascular abnormalities.[6] There is a high incidence of pulmonary hypertension in those patients with intracardiac shunts and congenital unilateral absence of a pulmonary artery.[14] Unilateral absence of one pulmonary artery is also frequently associated with tetralogy of Fallot.

Chest roentgenograms usually provide presumptive evidence of either pulmonary agenesis or hypoplasia. In the former condition, there is complete opacification of the involved side with shift of mediastinal structures to the affected hemithorax and with narrowing of the intercostal spaces on the affected side. The over-all appearance is identical to atelectasis of the lung. Compensatory emphysema of the opposite lung is invariably present. In cases of alveolar hypoplasia the findings are similar, but there is aerated lung identified on the affected side. The appearance of the chest may be confused with congenital lobar emphysema, and fluoroscopy may be of value in the differentiation. The emphysematous lung of congenital lobar emphysema does not deflate with expiration, whereas compensatory emphysema of the normal lung in patients with alveolar hypoplasia will not remain overinflated during expiration. In addition, infants with congenital lobar emphysema frequently have severe dyspnea, whereas infants with alveolar hypoplasia are usually asymptomatic. Duplication of the diaphragm may also simulate alveolar hypoplasia, but in all of these conditions angiocardiography will determine if the pulmonary artery to the affected side is absent or hypoplastic[18] (Fig. 7, *A* and *B*). In severe hypoplasia, compensatory dilatation of the pulmonary arteries on the opposite side may be striking. Bronchoscopy and bronchograms are usually unnecessary, uninformative and dangerous.

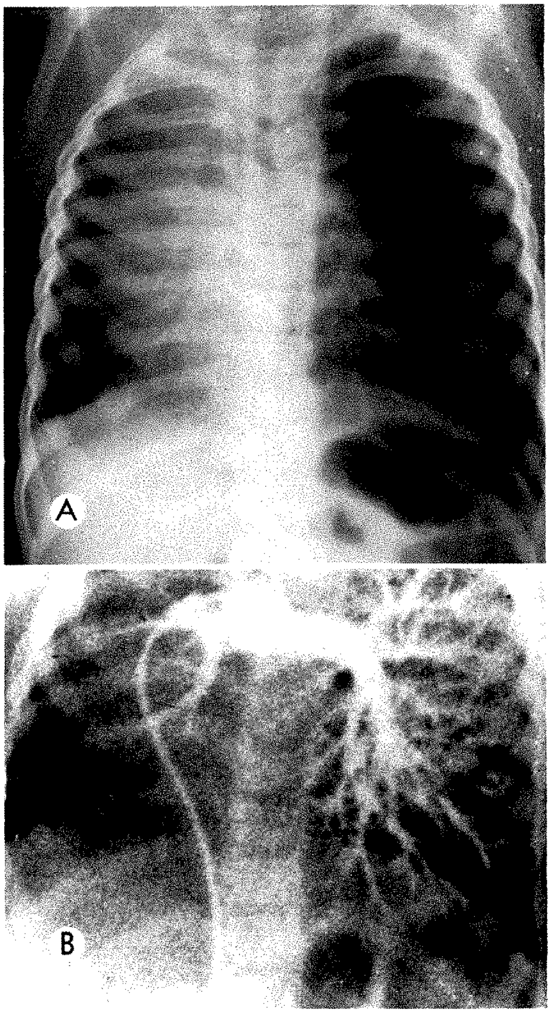

FIG. 7. Pulmonary hypoplasia in a 2 year old boy. (*A*) Anteroposterior chest roentgenogram shows shift of mediastinal structures to the right with a small right hemithorax and compensatory emphysema of the left lung. (*B*) Cineangiocardiogram shows increased vascularity of the left lung with small hypoplastic right pulmonary artery.

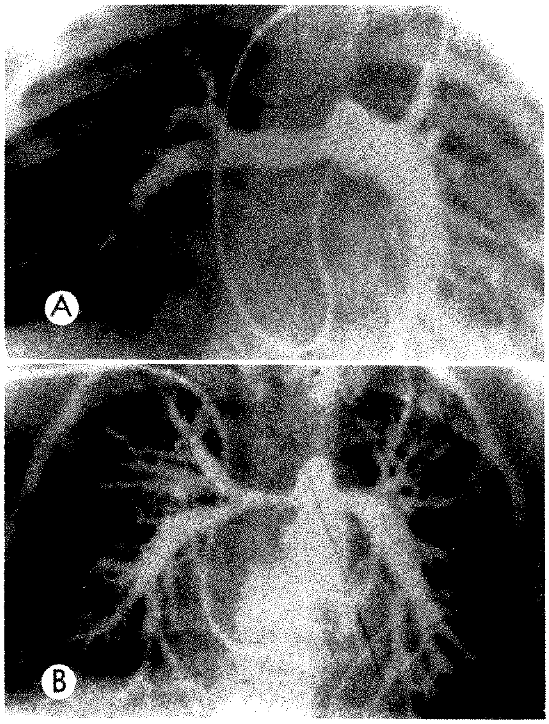

FIG. 8. Pulmonary artery branch stenoses. (*A*) Localized stenosis at origin of right main pulmonary artery in a 3 year old boy. (*B*) Bilateral pulmonary artery stenoses with poststenotic dilatation of the lobar branches in a 2 year old boy.

PULMONARY ARTERY BRANCH STENOSES

Stenotic lesions of the pulmonary arteries distal to the pulmonary valve, although rare, are being recognized more frequently with the increased usage of angiocardiography.[9,12] Gay *et al.*[7] have reported in detail the clinical and roentgenologic findings of the various types of pulmonary artery stenoses. Peripheral pulmonary artery stenoses may consist of (1) single, and multiple stenoses of lobar, segmental, or subsegmental sized arteries usually with poststenotic dilatation; (2) stenosis of one or both main branches of the pulmonary artery also with poststenotic dilatation; and (3) supravalvular stenosis of the pulmonary trunk. The mild forms of the condition usually remain unrecognized unless cardiac catheterization or angiocardiography is performed to evaluate an unexplained heart murmur. Severe cases may present confusing clinical manifestations, and other congenital lesions of the heart are frequently present. Auscultation reveals systolic murmurs in atypical locations and occasionally systolic and diastolic murmurs which may simulate aortic valvular stenosis or patent ductus arteriosus. Most often a systolic ejection murmur of long duration may be heard unusually well over the lateral aspect of the chest wall on the involved side. The clinical symptoms depend on the degree of obstruction to pulmonary blood flow and the increased work of the right ventricle. Cyanosis may occur if there is an associated ventricular or atrial septal defect. Cardiac catheterization is of value in demonstrating the increase in systolic pressure on withdrawal of the catheter from the distal to the proximal segment of the stenotic pulmonary arteries. A more precise diagnosis, however, can be made by the roentgenographic identification of the peripheral stenoses following selective angiocardiography of the pulmonary artery (Fig. 8, *A* and *B*). The presence of multiple pulmonary artery branch stenoses is apparently the result of abnormal channel development in the merging of the pulmonary buds from the sixth aortic arch with the postbranchial plexus.

RETROTRACHEAL LEFT PULMONARY ARTERY

Anomalies of position of the pulmonary artery are extremely rare. One variation of a left pulmonary artery which passed posterior to the trachea was reported by Wittenborg *et al.*[17] The embryologic explanation is unknown but presumably is the result of the formation of an anomalous vessel from the primitive vascular plexus about the esophagus and tracheal bud. The vessel compresses the trachea leading to symptoms of respiratory obstruction. Esophagrams will show an anterior defect at the left side of the esophagus just above the tracheal carina. In addition, there is increased separation of the trachea and esophagus at this level. Obstructive pulmonary emphysema may be identified on routine chest roentgenograms. We have not

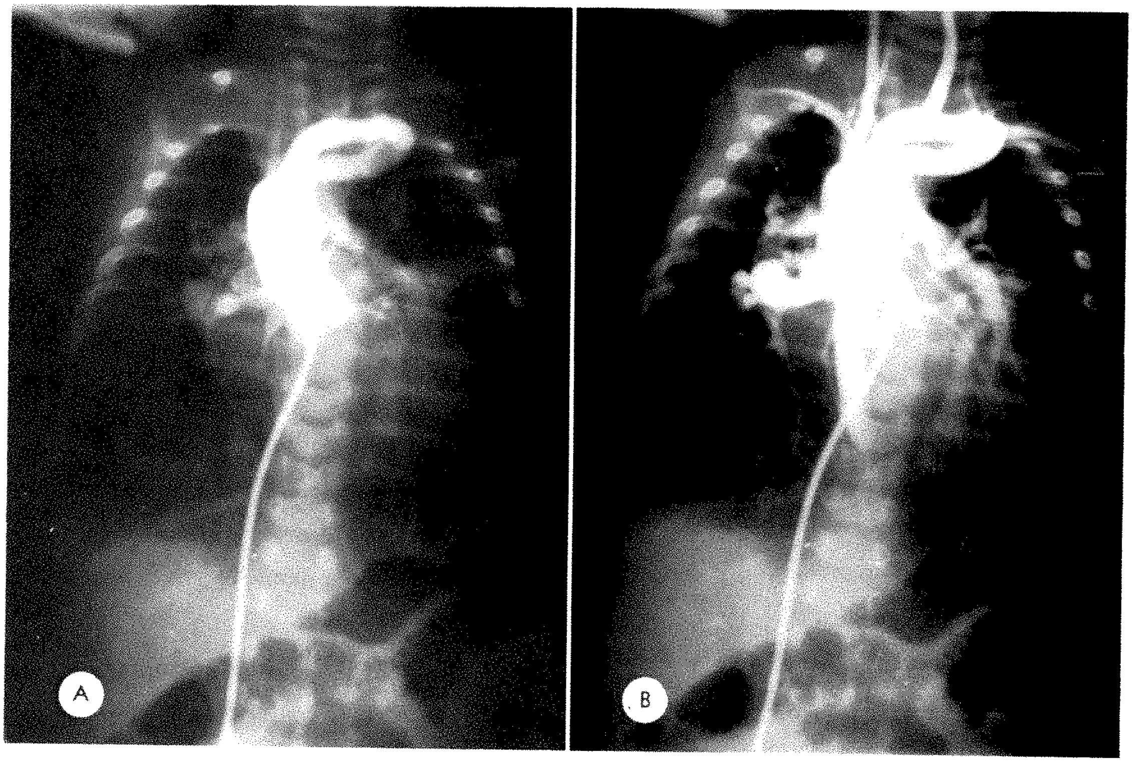

FIG. 9. Anomalous origin of the pulmonary artery in a 3 year old boy. (*A*) Catheter has been passed through the ventricular septal defect into ascending aorta. The aortic arch is on the right and a large opacified trunk extends to the left and inferiorly to bifurcate (*B*) and provide blood supply to the lungs.

had the opportunity of seeing similar patients in this institution.

ANOMALIES OF THE ORIGIN OF THE PULMONARY ARTERIES

A rare but interesting anomaly occurs when there is failure of development of the ventral portion of the sixth aortic arch with persistence of the sixth dorsal arch. This results in a large "ductal-like" vessel which has its origin from the aortic arch from where it passes to the mediastinum and divides into the right and left pulmonary arterial branches. The resulting clinical findings are dependent on the size of the vessels and the amount of pulmonary blood flow. If the blood flow is small, the clinical findings will be similar to those of Fallot's tetralogy, whereas if the blood flow is large the findings will be similar to those encountered in a true truncus arteriosus. The entire cardiac output passes into the aorta and the pulmonary arterial trunks divert a portion of this to the lungs. This anomaly is embryologically similar to unilateral absence of the pulmonary artery with associated anomalous origin of a single pulmonary artery. It is also similar to pulmonary artery atresia or pseudotruncus arteriosus; the major difference is that in pseudotruncus the pulmonary circulation is supplied by collaterals derived from the postbranchial plexus.

Chest roentgenograms usually show cardiac enlargement with increased pulmonary arterial markings in the lungs. A density may be seen in the left apex, this representing the persistent dorsal sixth arch. Angiocardiograms demonstrate the right aortic arch and the anomalous vessel arising from it extending into the apex of the left hemithorax and then tortuously passing inferiorly to divide into the pulmonary arteries (Fig. 9, *A* and *B*). Rarely, a similar anomalous vessel may be present on the right, apparently representing persistence

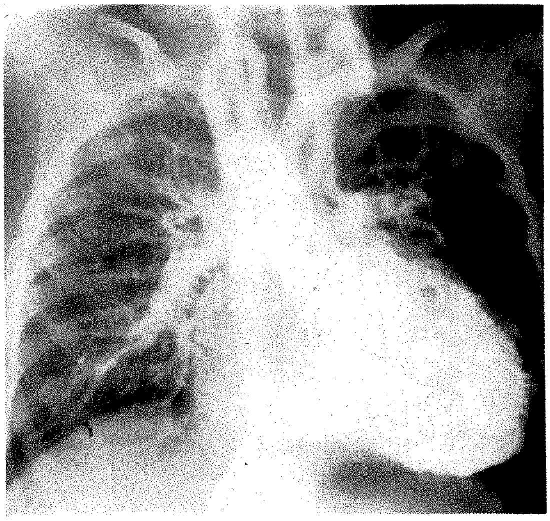

FIG. 10. Anomalous origin of the pulmonary arteries in an 8 week old boy. Contrast material has been injected into the right ventricle passing through ventricular septal defect to opacify the aortic arch which is on the right and gives rise to two large trunks which extend to the apex of each hemithorax and then pass inferiorly to each lung.

of the dorsal portion of the right sixth arch, and in turn passing inferiorly to form pulmonary arteries to the right lung (Fig. 10).

III. ABNORMALITIES OF THE PULMONARY VASCULAR BED

PULMONARY ARTERIOVENOUS FISTULA

Congenital arteriovenous communications involving the lungs are not uncommon. The patients may be asymptomatic but frequently there is evidence of arterial hemoglobin desaturation as manifested by polycythemia, clubbing and occasionally cyanosis. Routine chest roentgenograms may be diagnostic by demonstrating the dilated vascular channels extending from the hilar area to a more homogeneous area of density representing the arteriovenous communication. Laminagrams may also be of value in demonstrating the afferent and efferent vessels but the most reliable and confirmatory method of demonstration is by angiocardiography. Opacification of the vascular pathways to and from the arteriovenous fistulae is diagnostic and frequently additional fistulae may be identified which were not suspected prior to angiocardiography (Fig. 11, *A* and *B*).

PULMONARY ARTERIAL SCLEROSIS

Abnormalities of the pulmonary vascular bed also include medial hypertrophy, sclerosis, vasculitis and thromboembolism The most frequent abnormality is atherosclerotic lesions on the intimae of the large elastic arteries. These sclerotic lesions consist of localized yellow plaques. They are quite frequently found in patients with pulmonary hypertension and occur in older individuals without pulmonary hypertension. The physiologic counterpart of these lesions is apparently not significant, since they produce little or no obstruction.

The large and small muscular arteries present a spectrum of structural abnormalities. The most important are those occurring in the small muscular arteries which, by definition, are those arteries measuring 100 μ in diameter or less. It is important that these small muscular arteries be differentiated from the arterioles which may have the same size but a different anatomic configuration. The muscular artery, by definition, has an internal and external elastic membrane and a discrete layer of muscle. The arteriole, in contrast, has an intimal layer and an indistinct layer of elastic membrane. No discrete muscle layer is encountered. There is no way of distinguishing an arteriole from a venule unless the attachment of the vessel to an artery or a vein is identified.

The simplest and most common abnormality of the small muscular arteries is an increased thickness of the media. This is encountered in every fetus and newborn and may persist normally until about the age of 6 weeks. Medial hypertrophy is also encountered pathologically in association with congenital malformations of the heart, associated with increased pulmonary blood pressure with or without an increase in pulmonary blood flow. The second pathologic reaction is one of endothelial hyperplasia. This is encountered in malformations in which there is an increased pulmonary

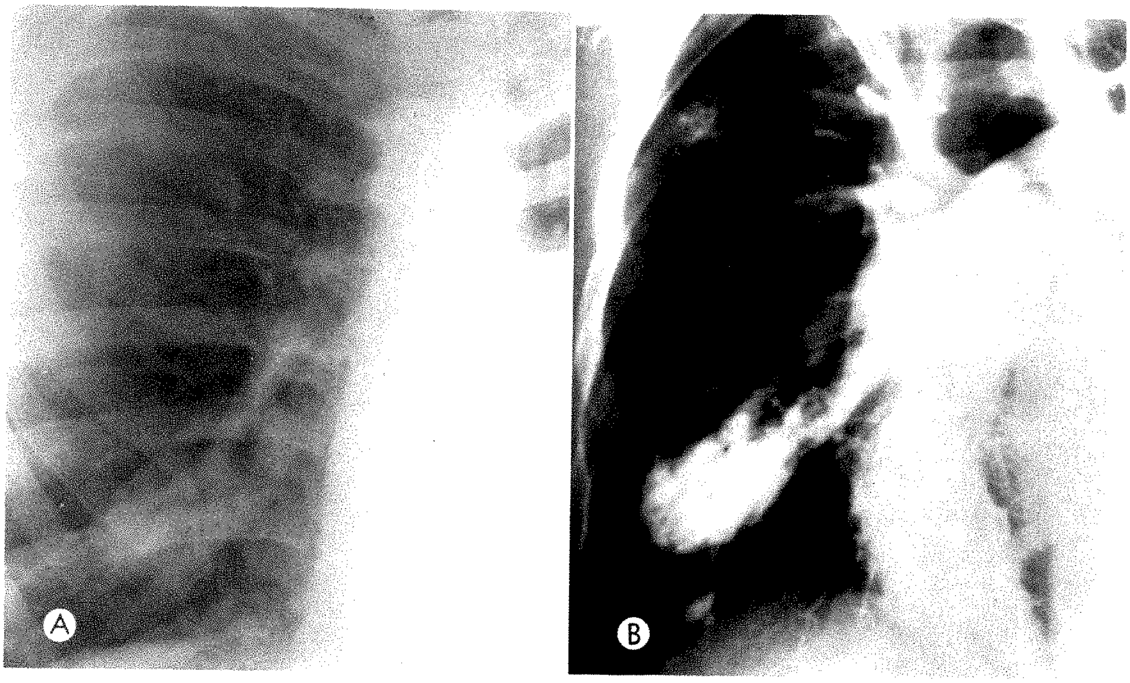

Fig. 11. Arteriovenous fistula in a 10 year old girl. (*A*) Posteroanterior chest roentgenogram shows density in right base. (*B*) Angiogrcardiogram shows opacification of arteriovenous fistula in the right lower lobe, as well as a similar unsuspected fistula in the right upper lobe.

blood pressure. This is a relatively uncommon finding and may represent a fleeting episode in the development of more advanced lesions. The most common abnormalities are the development of eccentric areas of sclerosis in the intima of large and small muscular arteries. In contrast to medial hypertrophy, which is uniform and concentric, intimal sclerosis is a localized patchy lesion with a capricious pattern of involvement. The involvement varies from minimal localized patches involving one segment of the circumference of a vessel to complete obliteration of the lumen. Other abnormalities which could be included with the sclerotic lesions consist of focal aneurysmal dilatations of the vessels due presumably to focal rupture of the elastic membranes and destruction of the muscular segment of the wall. Another form of intimal disease is the formation of multiple small blood vessels in the angiomatoid pattern. A final apparent reactive form is a vasculitis which may involve the large and small muscular arteries. There is necrosis of the vascular wall associated with an inflammatory response and the etiology is unknown.

The previously described lesions of medial hypertrophy, intimal sclerosis, and vasculitis are associated with pulmonary hypertension. The increased pressure may or may not be associated with increased flow and increased pressure while the intimal lesions are associated with increased pressure and normal or even decreased flow. The cause and effect relationships are entirely conjectural. It is the working hypothesis in this laboratory that the medial hypertrophy represents a persistence of the fetal configuration in the presence of an increased pressure and flow through the lung. It is possible that the medial hypertrophy becomes responsible for the sustained high pulmonary arterial blood pressure. The intimal lesions are considered to be a result of the hypertension although, as obstacles to flow, they may maintain and aggravate the level of pulmonary hypertension.

Another form of vascular lesion is made

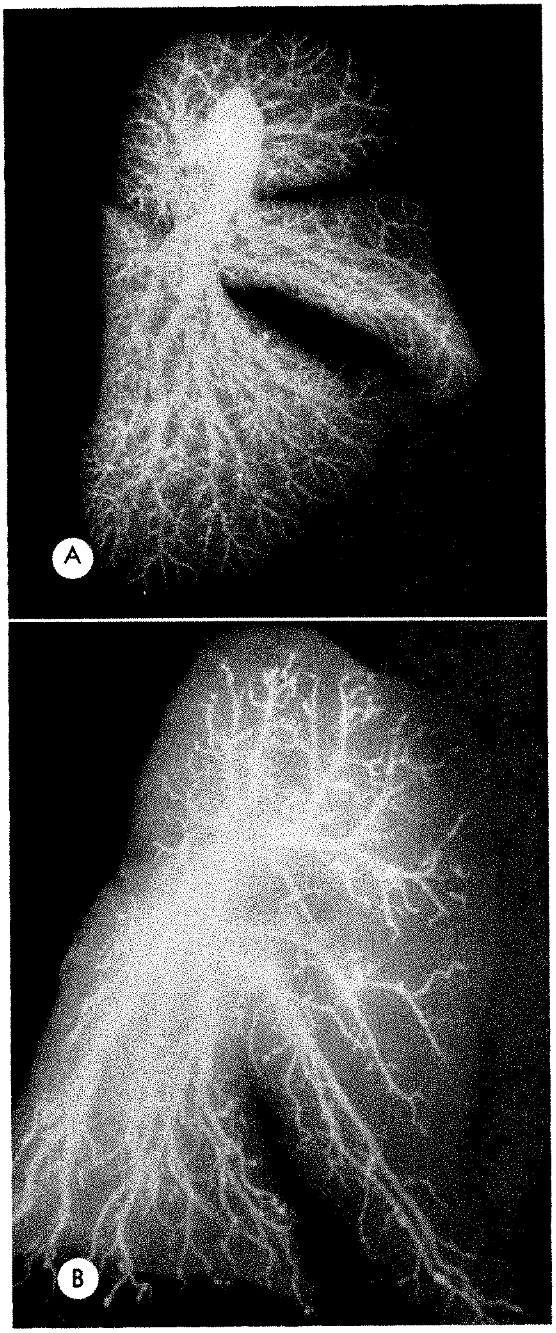

Fig. 12. Postmortem specimens. (*A*) Arteriogram of normal postmortem lung. Distal ramifications are clearly outlined. (*B*) Arteriogram of patient with intimal sclerosis showing abrupt termination of the smaller arteries producing "pruned-tree" appearance.

up of multiple thrombi in varying degrees of organization seen with decreased pulmonary flow. This is classically encountered in tetralogy of Fallot. In this case, the pulmonary vascular bed is not associated with an increased pressure and is associated with a decreased flow.

There is at least one group of workers who consider all of the intimal lesions associated with pulmonary hypertension as the result of thromboembolism.

From examination of postmortem pulmonary arteriograms, the pattern of the vascular bed is not discernibly different in those individuals with an increased blood flow and pressure associated with medial hypertrophy and the normal. This is interpreted as the lack of physiologic vascular tone in the postmortem specimen. The medial hypertrophy is thus considered to be a spastic or tonic mechanism rather than a true anatomic abnormality. This is inter-

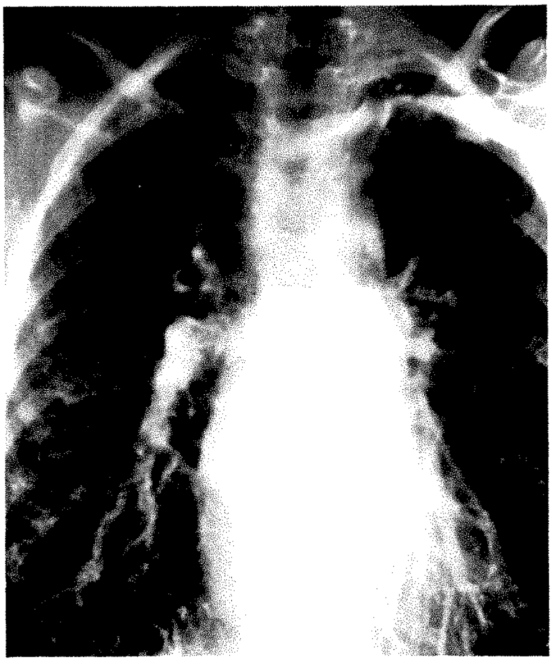

Fig. 13. Pulmonary telangiectasia in a 7 year old girl. Angiocardiogram shows opacification of multiple small arteriovenous fistulae.

preted as evidence for the reversibility of this lesion. In contrast, by angiography, the intimal lesions are readily discernible as obstructing the large and small pulmonary vessels (Fig. 12, *A* and *B*). This is interpreted as demonstrating the truly obstructive potential of this form of lesion.

PULMONARY TELANGIECTASIA

Multiple minute congenital arteriovenous communications involving the lung may occur as a manifestation of the Osler-Weber-Rendu disease.[3] The clinical manifestations are similar to other forms of pulmonary arteriovenous fistulae; namely, cyanosis, polycythemia, dyspnea, and clubbing of the fingers. Visible hemangiomata of the skin and oral mucous membranes are usually present.

Chest roentgenograms show vascular markings which may be more prominent than usual and frequently have a reticular pattern. Angiocardiography is of value in opacifying the minute small hemangiomas (Fig. 13).

SUMMARY

The classification of abnormalities of the pulmonary arteries is presented with a description of the embryology, clinical and roentgenographic findings of each condition. Many of these lesions are surgically correctable and others are of no clinical significance. Angiocardiography is the most reliable method of detection.

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ABSENCE OF THE PULMONARY VALVE IN THE TETRALOGY OF FALLOT*

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CONGENITAL pulmonary valvular insufficiency is uncommon. In most instances, there is an absence of mature pulmonary valvular tissue, although primitive connective tissue may reside at the expected location of the valve. In other cases, regurgitation results from defective formation of identifiable pulmonary valvular cusps. Congenital pulmonary valvular insufficiency, regardless of the specific appearance of the pulmonary valve, has frequently been termed "absence of the pulmonary valve." Although absence of the pulmonary valve may occur as an isolated cardiac anomaly, it usually is associated with a ventricular septal defect. In this case, the internal architecture of the heart is usually that of the tetralogy of Fallot.

There are unique clinical features which characterize cases of pulmonary insufficiency and the tetralogy of Fallot. The most diagnostic of these are the rough to-and-fro murmurs and the characteristic roentgenographic findings.

This communication is a report on 2 infants whose clinical, angiocardiographic, and pathologic features typify the findings of absence of the pulmonary valve in association with the tetralogy of Fallot.

CLINICAL FINDINGS

The clinical manifestations of the 2 cases will be described together since these were similar in each (Table I).

The history is that of cyanosis appearing in the first week of life followed shortly by the onset of respiratory distress. Both the cyanosis and respiratory distress increased progressively.

TABLE I

SIGNIFICANT CLINICAL FEATURES

Clinical Findings	Case I	Case II
Age	2 days	2½ weeks
Sex	Female	Female
Neonatal Cyanosis	+	+
Respiratory Distress	+	+
Bronchial Obstruction	○	+
Systolic and Diastolic Thrills	+	+
To-and-Fro Murmurs	+	+
Single Second Sound	+	+
Electrocardiogram	RVH[φ]	RVH[φ]
Roentgenography	APT*	APT*

+ = present; ○ = absent; [φ]RVH = marked right ventricular hypertrophy; *APT = aneurysmally dilated pulmonary trunk.

Each patient was referred to the University of Minnesota Hospitals, Case I at the age of 2 days and Case II at 2½ weeks.

Physical examination revealed moderate to marked cyanosis. Respiratory distress was exemplified by rapid respiratory rates, abdominal breathing, and over-expansion of the thorax accompanied by intercostal retraction. In Case I inspiratory and expiratory wheezes were heard over the right hemithorax.

Prominent rough systolic and diastolic murmurs, to-and-fro in character, and associated with systolic and diastolic thrills, were present in each. The systolic murmur was harsh and of the ejection type. This murmur and its associated thrill were of maximal intensity along the left sternal border. The diastolic murmur which was rough and decrescendo and the associated thrill were most intense at the left second intercostal space anteriorly. The second cardiac sound was single, and loudest at the

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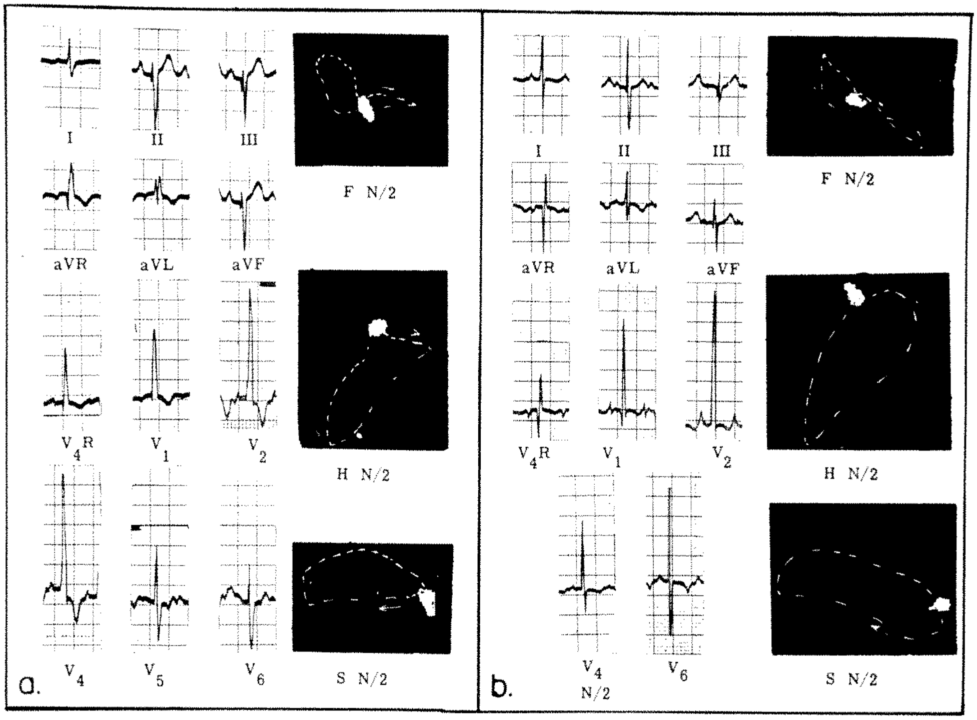

Fig. 1. (*a* and *b*) Electrocardiogram and vectorcardiogram in Cases I and II, respectively. Representative electrocardiographic leads are on the left and vectorcardiographic loops are on the right in each case. F = frontal plane; H = horizontal plane; S = left sagittal plane. Arrows indicate direction of inscription of the loops. N/2 = one/half standardization. (*a*) Case I, 12 day old-girl. Marked right axis deviation, qR pattern in leads V_4R and V_1 and large S wave in lead V_6 indicate marked right ventricular hypertrophy. The clockwise inscription of the QRS sE loops in 3 planes and the anterior, right, and superior orientation of the loop confirm the diagnosis of marked right ventricular hypertrophy. (*b*) Case II, 3 week old girl. The mean QRS axis is indeterminate in the limb leads. Marked right ventricular hypertrophy is suggested by the qR patterns in leads V_4R and V_1 and the large S wave in lead V_6. Left ventricular hypertrophy is also suggested by the tall R wave in lead V_6 and by the leftward displacement of the first part of the QRS sE loop in the frontal and horizontal plane. Peaked P waves in lead V_2 suggest right atrial enlargement.

lower left sternal border in each case. In Case II, additionally, a systolic ejection click was heard at the apex and along the lower left sternal border. Hepatomegaly was present in each case.

Electrocardiograms and vectorcardiograms were available for review in each case (Fig. 1, *a* and *b*). These showed signs of right ventricular hypertrophy with qR patterns in leads V_4R and V_1 and large S waves in lead V_6. These patterns were associated with a clockwise inscription of the QRS sE loops in the frontal, horizontal, and saggital planes. In addition, in Case II, there were signs of right atrial enlargement and a tall R wave in lead V_6, suggesting left ventricular hypertrophy.

Cardiac catheterization was performed in Case II. In this procedure, which was done under local anesthesia, the course of the catheter was unusual. When the catheter tip was in the right ventricular infundibulum, its position corresponded with the left border of the cardiac shadow. As the catheter was advanced, it turned cephalad and medially toward the midline where the pulmonary valve (with gradient of pressure) was considered to be present. Immediately beyond this level, the catheter tip entered a large aneurysmal-like segment in the pulmonary arterial system. The catheter could not be advanced into the peripheral pulmonary arterial branches but became coiled in the dilated pulmonary ar-

TABLE II

SYNOPSIS OF CARDIAC CATHETERIZATION DATA IN CASE II

Sampling Site	Pressure (mm. Hg)	Oxygen Saturation (per cent)
Superior Vena Cava	—	30
Right Atrium	a = 17; M = 10	31
Inferior Vena Cava	—	36
Left Atrium	a = 17; M = 13	45
Right Ventricle	80/8–15	—
Pulmonary Artery*	40/12; M = 22	30
Right Femoral Artery	—	49

* Catheter tip in aneurysmally dilated pulmonary artery. M = mean; a = a wave.

Note: Characteristics of tetralogy of Fallot are systemic levels of pressure in right ventricle, pressure gradient across the pulmonary valvular ring, and peripheral arterial desaturation.

tery. Studies of pressures indicated right ventricular hypertension and pulmonary stenosis (Table II). The pulmonary arterial systolic and mean pressures were elevated but the systolic pressure was less than the corresponding right ventricular pressure.

The records of pulmonary arterial pressures revealed a wide pulse pressure and absence of a dicrotic notch. These findings were considered to be compatible with pulmonary insufficiency. High end-diastolic pressure in the right ventricle corresponded with tall a waves in the right atrium.

Angiocardiographic procedures were performed in each case and will be described separately.

The working diagnosis in each patient, based primarily on the physical and roentgenographic findings, was the tetralogy of Fallot with pulmonary insufficiency. The condition of each patient was precarious throughout the hospital stay and, in each, congestive cardiac failure was only partially controlled. The first patient died at the age of 2 weeks while the second died at the age of 3 months.

ROENTGENOLOGIC FINDINGS

The details in the 2 cases will be described separately.

Case I. In this patient roentgenograms of the thorax showed moderate cardiomegaly with a prominent convexity of the left upper cardiac border. The peripheral pulmonary vasculature appeared normal, but the central vasculature (particularly at the right hilus) was prominent (Fig. 2, *a* and *b*). The central pulmonary vasculature was noted to pulsate vigorously during roentgenoscopy.

Forward angiocardiography was performed from the saphenous vein and serial roentgenograms were taken in frontal and lateral projections. These showed sequential filling of the inferior vena cava, right atrium, a large right ventricle, and a huge, dilated, and pulsating infundibulum. A constriction of mild degree was noted at the junction between the infundibulum and the dilated pulmonary trunk (Fig. 2, *c* and *d*).

Case II. In this case, the thoracic roentgenograms presented an unusual finding (Fig. 3, *a* and *b*). A large, round, right hilar density projected into the right hemithorax. Although it suggested a tumor, the vigorous pulsation of this mass (noted during roentgenoscopy) indicated that it was vascular in nature. The upper aspect of the left cardiac border bulged prominently and there was moderate cardiomegaly.

Selective right ventricular angiocardiography was performed in conjunction with the cardiac catheterization already described. Serial roentgenograms were made in frontal and lateral projections. Angiocardiograms showed sequential filling of a large right ventricle and a long infundibulum (Fig. 3, *c* and *d*). Both of these structures seemed to be rotated toward the left, so that the infundibulum curved medially and to the right. It terminated in the orifice of the pulmonary trunk, which lay in a sagittal plane at the midline. This was followed by opacification of a strikingly enlarged pulmonary trunk which extended into the right hemithorax and represented the peculiar right hilar density noted on the conventional roentgenograms. The pulmonary trunk displayed rhythmic dilatation and constriction with ventricular systole and ventricular diastole, respectively.

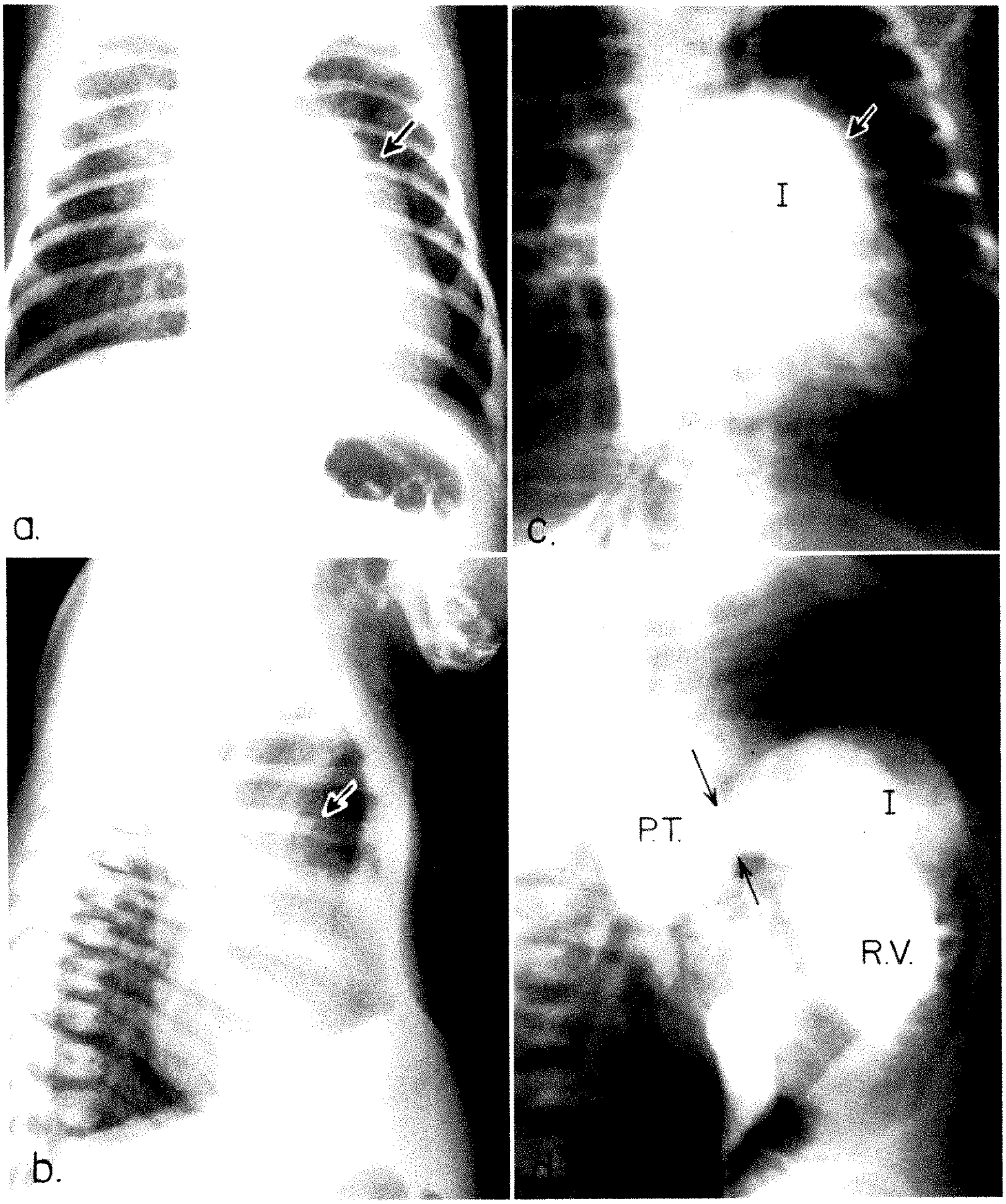

Fig. 2. Roentgenologic features in Case 1. (*a* and *b*) Frontal and lateral roentgenograms of the thorax. Cardiomegaly and marked prominence of the upper left cardiac border which represents a markedly enlarged infundibulum (arrows). (*c* and *d*) Forward angiocardiograms (from saphenous vein) in frontal and lateral views, respectively. Sequential opacification of the inferior vena cava, right atrium, an enlarged right ventricle (R.V.), infundibulum (I), and pulmonary trunk (P.T.). In the frontal view arrow points to infundibulum of the right ventricle. In the lateral projection the location of the pulmonary valvular annulus is indicated by small facing arrows.

In addition to the above findings, simultaneous opacification of the pulmonary trunk and aorta from the right ventricle was observed, indicating the presence of a ventricular septal defect and a right-to-left shunt.

PATHOLOGIC FINDINGS

Case I (Fig. 4, *a–d*). Viewing the exterior of the heart and great vessels, the most unusual finding was the marked prominence of the right ventricular infundibulum. The pulmonary trunk and its right and left branches were uniformly dilated. The aortic arch was on the right side.

The interior of the heart showed the fundamental anatomic features of the tetralogy of Fallot. There was a long, dilated, infundibular tract which narrowed at the pulmonary valvular ring (0.4 cm. in diameter). Beyond this the pulmonary trunk was dilated (0.8 cm. in diameter).

At the expected location of the pulmonary valve, there was a ring of nodular, gelatinous tissue which represented rudimentary valvular tissue.

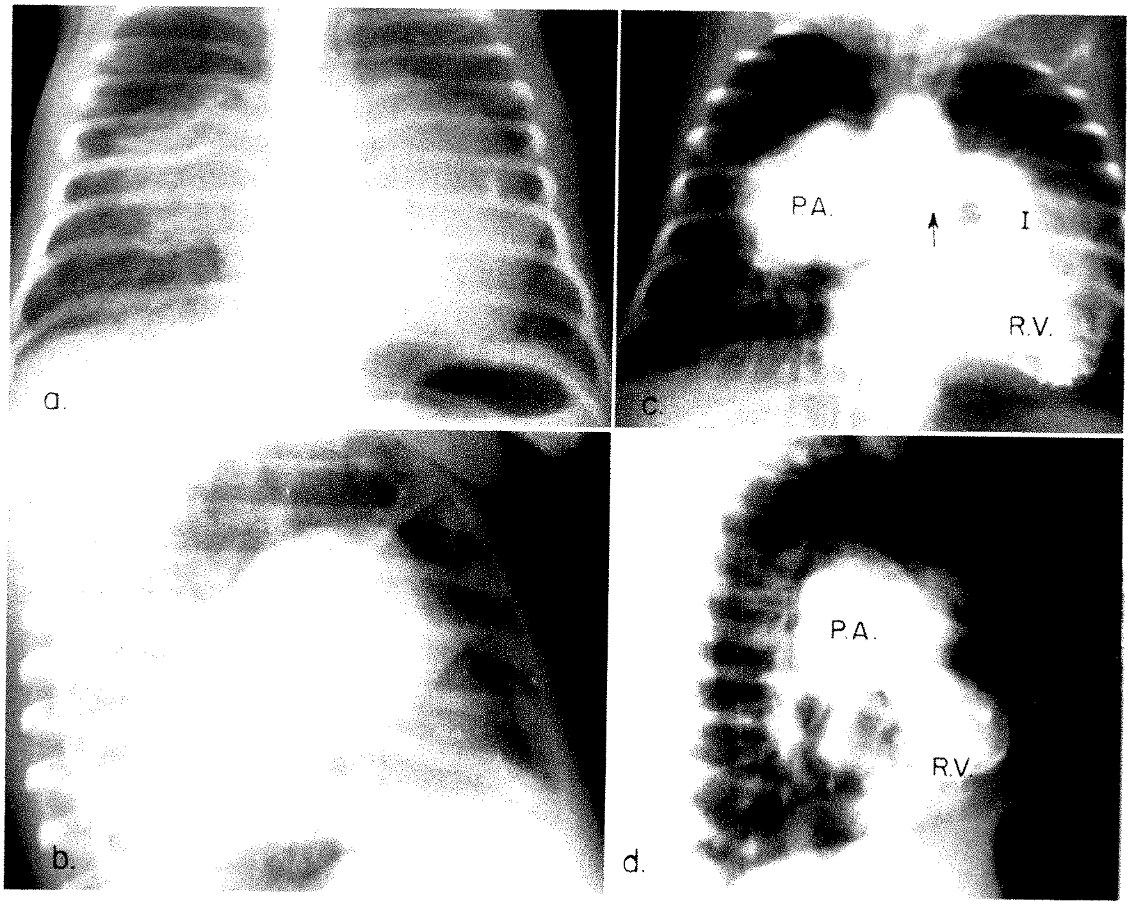

FIG. 3. Roentgenologic features in Case II. (*a* and *b*) Frontal and lateral views, respectively, of thoracic roentgenograms. Cardiomegaly with marked prominence of the upper left cardiac border. This prominence represents an enlarged, levorotated infundibulum. The large, rounded, hilar density extending into the right hemithorax seen in the frontal view is also apparent in the lateral view and represents an aneurysmal dilatation of the pulmonary trunk. (*c* and *d*) Selective angiocardiograms from the right ventricle. The right ventricle (R.V.) is enlarged. The infundibular tract (I) and the huge pulmonary trunk (P.A.) are opacified. The location of the pulmonary valvular annulus is marked with an arrow in the frontal view. The aorta opacifies from the right ventricle indicating the presence of a ventricular septal defect with right-to-left shunt.

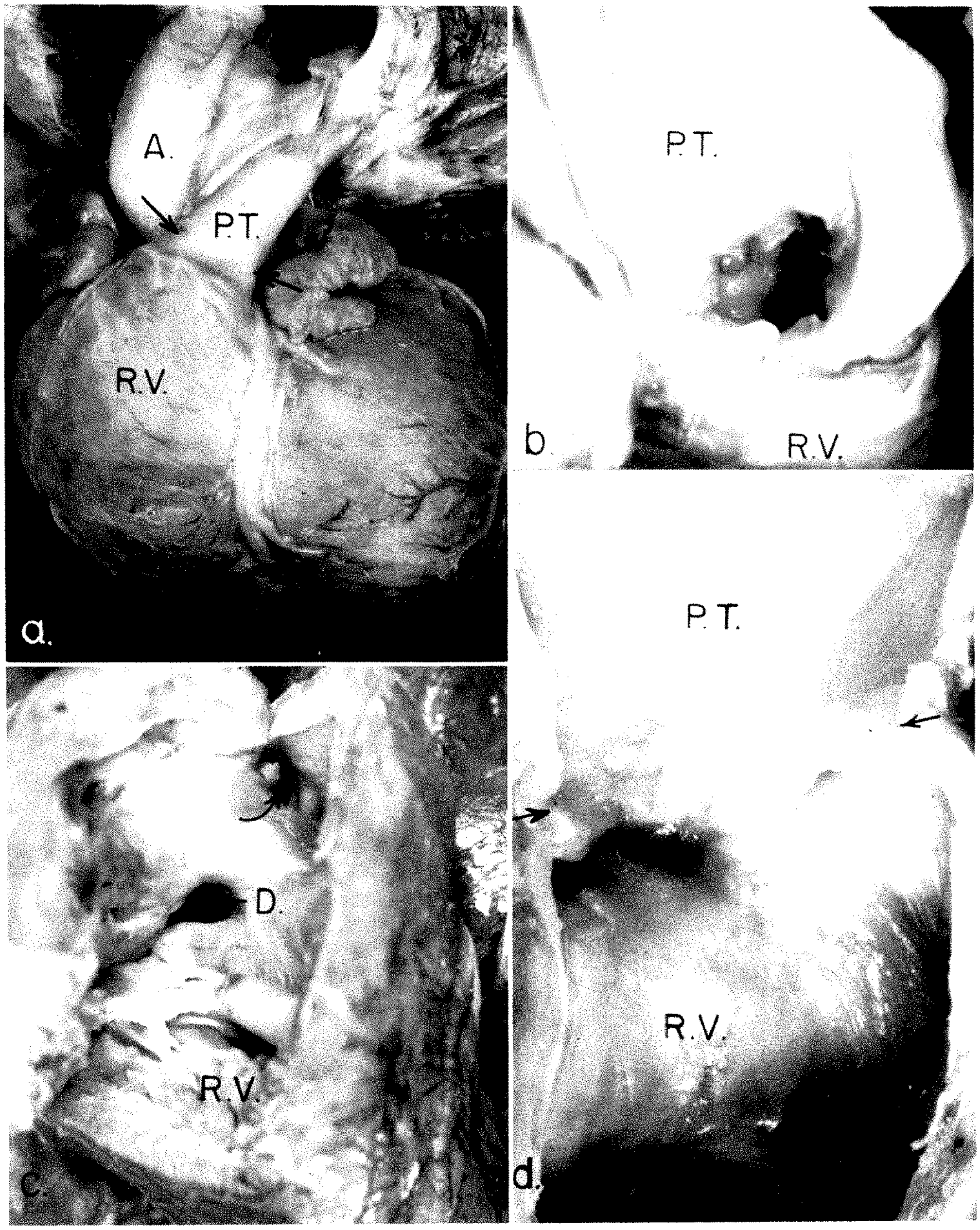

Fig. 4. Gross pathologic features in Case 1. (*a*) External view of left anterior aspect of the heart and great vessels. Marked prominence of the dilated right ventricular infundibulum (R.V.). The pulmonary trunk (P.T.) is uniformly dilated, as were its branches. Zone of constriction (arrows) at origin of pulmonary trunk. The aortic (A.) position is normal. (*b*) Interior of the origin of the pulmonary trunk (P.T.) viewed from above. At the anticipated location of the pulmonary valve, the orifice narrows and tags of primitive connective tissue protrude into the lumen. R.V. = exterior of right ventricle. (*c*) Interior of right ventricle (R.V.). A ventricular septal defect (D.) over which the aorta arose. The vertically oriented crista supraventricularis creates a long infundibular tract. Arrow points to narrow orifice at origin of pulmonary trunk as viewed from below. (*d*) Right ventricle (R.V.) and pulmonary trunk (P.T.) have been opened. Facing arrows point to constriction of pulmonary arterial origin. At the expected location of the valvular cusps, there is a ring of rudimentary, gelatinous connective tissue.

Histologically, at the expected area of the pulmonary valve, no mature valvular tissue was present. In this location there was, however, a large avascular mass of pale-staining, highly cellular primitive connective tissue which projected slightly into the lumen.

The structure of the media of the pulmonary trunk was grossly irregular. The fibers lacked the usual parallel arrangement. Instead, they were oriented in many directions. In some areas groups of fibers ran parallel and at odd angles to other such groups, giving a mosaic pattern to the elastic elements of the media.

Case II (Fig. 5, *a–d*). Viewed externally, the right ventricle and its infundibulum were enlarged. The infundibulum was separated from the aneurysmally dilated pulmonary trunk by a constriction at the anticipated location of the pulmonary valve (Fig. 5*a*).

The internal arrangements of the heart were those of the tetralogy of Fallot but with the aorta taking a greater than average portion of its origin from the right ventricle. The tortuous, infundibular channel (0.7 cm. in diameter) narrowed considerably at the constricted pulmonary valvular ring of which the diameter was 0.4 cm. The dilated pulmonary trunk above the constriction measured 2 cm. in diameter. Neither a pulmonary valve nor remnants of mature valvular tissue were present. As in Case I, irregular, gelatinous tissue ringed the pulmonary valvular annulus. In addition, there was a tiny sinus pocket (Fig. 5*b*) in the pulmonary trunk above the annulus. This may have represented a rudimentary pulmonary valvular sinus.

Unfortunately, the branches of the pulmonary trunk were not present in the specimen submitted to us. This precluded a close correlation of the pathologic findings with angiocardiographic observation of an aneurysmally dilated right pulmonary artery.

Histologically, primitive valvular tissue similar to that in Case I was found lining the pulmonary valvular ring (Fig. 6, *a* and *b;* and 7). A diverticulum-like recess extended laterally through the lowermost portion of this primitive tissue. The morphologic arrangement at the area of the rudimentary sinus pocket differed from that of the remaining valvular ring. It was represented by a thin pouch-like protrusion of the pulmonary arterial wall.

In the media of the pulmonary trunk, a tendency for a parallel arrangement of the elastic fibers was noted just beneath the intima and adventitia. In the intervening zone an irregular arrangement of elastic fibers with a tendency toward a mosaic pattern was present, as in Case I.

COMMENT

Congenital pulmonary insufficiency has been found more frequently with ventricular septal defect than as an isolated condition. Of the 38 cases of congenital pulmonary valvular insufficiency reported since 1908[1–21] (including the 2 cases in this communication), 27 cases had an associated ventricular septal defect.[1,3,4,7,8,12,13,15–17,19–21] Twenty of these 27 cases exhibited the anatomic features of the tetralogy of Fallot. In the 11 cases with no ventricular septal defect, the pulmonary valvular insufficiency was an isolated condition[2,5,6,9–11,14,18] (including cases of 2 children with a patent ductus arteriosus). In Table III the bibliographic source, the association of ventricular septal defect, and methods used in diagnosis in the 38 known cases of congenital pulmonary valvular insufficiency are summarized.

Clinically, patients with ventricular septal defect and pulmonary valvular insufficiency usually present as mildly cyanotic infants or young children. They frequently manifest cardiac decompensation and die at an early age.

The diagnostic features of congenital pulmonary valvular insufficiency associated with ventricular septal defect which were exemplified in our 2 patients (Table I) include: (1) harsh, to-and-fro, systolic-diastolic murmurs and thrills along the left sternal border; (2) mild to moderate cyanosis; (3) vector and electrocardiographic

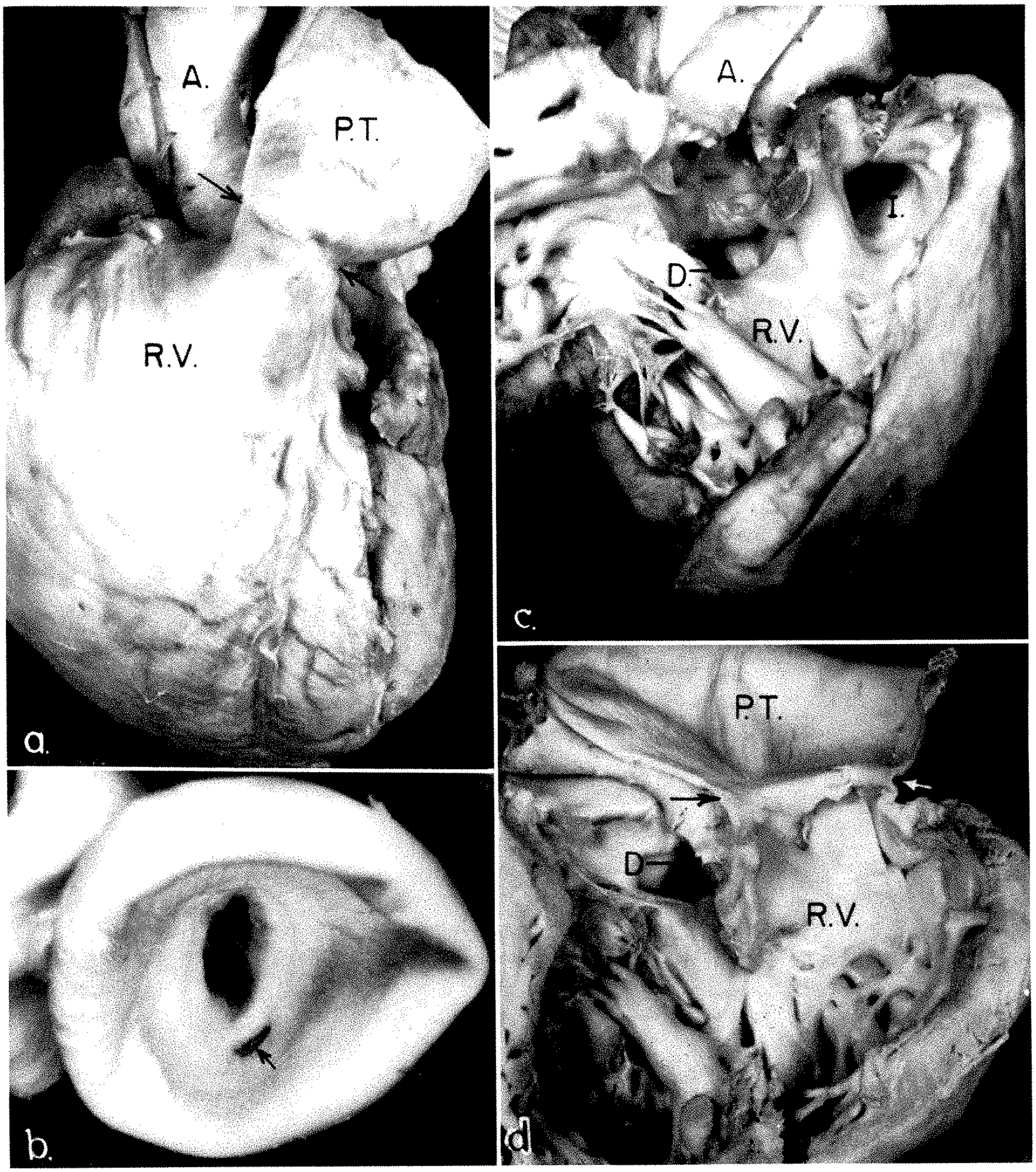

Fig. 5. Gross pathologic features in Case ii. (*a*) Exterior of anterior aspect of the heart. The right ventricle (R.V.), demarcated by the anterior descending coronary artery, is very large. At the anticipated location of the pulmonary valve, there is a constriction (facing arrows). Distal to this constriction, the pulmonary trunk is markedly dilated. (*b*) Interior of pulmonary trunk viewed from above. There is a constricted zone corresponding to the constriction shown externally in *a*. Above this a tiny blind pocket (arrow) protrudes from the pulmonary arterial wall. (*c*) Interior of the right ventricle (R.V.) of which the chamber is enlarged. Characteristic features of Fallot's tetralogy with a ventricular septal defect (D.) over which the aorta (A.) arises, and a vertical crista supraventricularis forming part of the wall of a long infundibular channel (I.). (*d*) The infundibulum of the right ventricle (R.V.) and the pulmonary trunk (P.T.) have been opened. There is no pulmonary valve. At the anticipated location of the valve, there is a ring of rudimentary, gelatinous tissue. The constriction at the valvular ring is marked with facing arrows. D = ventricular septal defect.

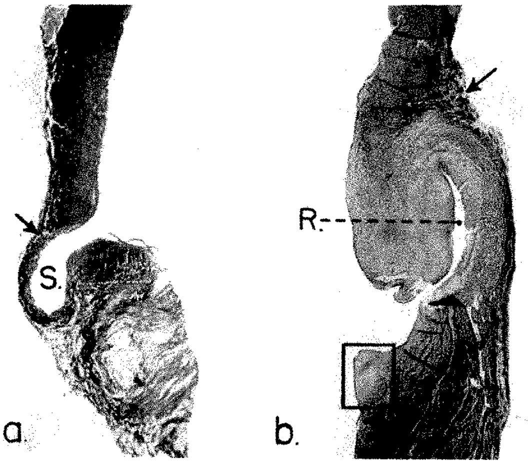

FIG. 6. Case II. Low power photomicrographs of longitudinal sections made from facing sides of the junction of the pulmonary trunk with the right ventricle. The luminal side of each section faces the corresponding side of the other. (*a*) A small, rudimentary sinus pocket (S.) lies at the origin of the pulmonary trunk. At the uppermost level of the ventricular myocardium, there is a large mass of pale-staining cells which resembles primitive connective tissue. This primitive tissue is located beneath the sinus and extends slightly into the lumen of the right ventricle. Arrow points to the zone of constriction which was noted grossly at the origin of pulmonary trunk (Fig. 5). (Elastic tissue stain × 10.) (*b*) A recess (R.) extends into the junction of the pulmonary trunk and right ventricle. The recess is overhung by a large mass of primitive valvular tissue. There is also a smaller mass of primitive connective tissue (rectangle) in the endocardium of the upper part of the right ventricle. Arrow as in *a*. The picture here is representative of the major part of the circumference of the junction of the pulmonary trunk and right ventricle. (H&E × 10.)

changes consistent with right atrial enlargement, and marked right ventricular hypertrophy (the latter usually of the systolic [pressure] overload type); and (4) certain roentgenologic findings. These include prominence of the hilar density caused by aneurysmally dilated and pulsating main pulmonary arteries. In addition to cardiomegaly, a prominent bulge at the upper left cardiac border representing the dilated outflow tract of the right ventricle is common. The peripheral pulmonary vascularity is usually normal. During roentgenoscopy the hilar density is seen to pulsate in rhythm with the heart, identifying it as a vascular structure. Since the appearance of the hilar density may easily be mistaken for a tumor, an awareness of this anomaly is important for its recognition.

Angiocardiography is the most useful diagnostic study in this condition. It may be performed from a peripheral vein (as in Case I) or selectively, from the right ventricle (as in Case II).

The anatomic features and fundamental hemodynamic states in this condition are readily defined by these procedures.

The angiocardiographic study identifies the hilar density as a massively dilated pulmonary trunk, or as main pulmonary arterial branches. Also visualized is the dilated right ventricular infundibulum. Early opacification of the aorta, immediately following visualization of the right ventricle,

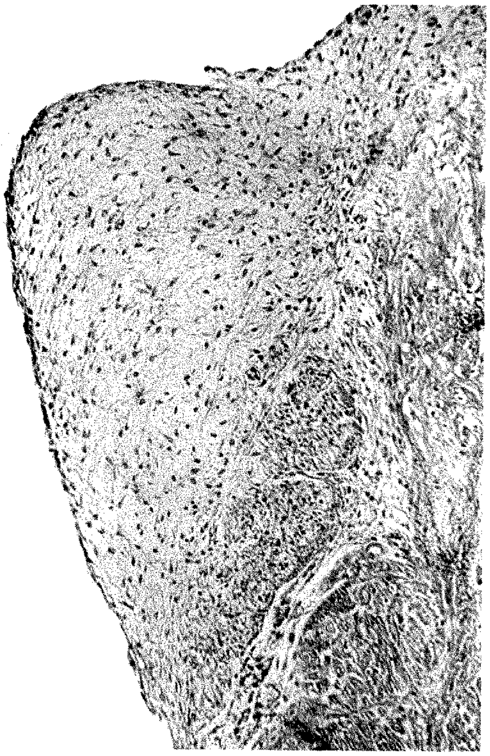

FIG. 7. Photomicrograph of zone in rectangle in Figure 6*b*. The tissue is highly cellular and avascular with cells resembling primitive connective tissue. (H&E × 150.)

TABLE III

SUMMARY OF 38 CASES OF CONGENITAL PULMONARY VALVULAR INSUFFICIENCY REPORTED IN THE LITERATURE

Associated Conditions	No. of Cases			Means of Diagnosis (by bibliography number)*			
	Total†	Male	Female	Cardiac Catheterization	Angiocardiography	Surgery	Necropsy
Ventricular Septal Defect without Pulmonary Stenosis	7	3	2	7	—	—	3, 7, 17, 20, 21
Ventricular Septal Defect with Pulmonary Stenosis	20	14	4	1, 4, 7, 8, 15, 19–II	4, 8, 15–I, II	8, 15, 19	1, 4, 7, 8, 12, 13 15, 17, 19, 21–I, II
Intact Ventricular Septum	11	8	1	5, 9, 11, 14, 18	5, 9	6	10, 19, 21

* Roman numerals I and II indicate case numbers in this communication.

† The sex was not stated in 6 cases.[21]

indicates the presence of an associated ventricular septal defect and pulmonary stenosis, features of the tetralogy of Fallot.

The prognosis of pulmonary valvular insufficiency with ventricular septal defect is poor. Of the 27 reported cases, 23 patients had died by the time they were reported and 10 of these were less than 17 months of age. Eleven of the 27 were from 3 to 11 years old at the time of death, while 2 were adults (death at ages 32 and 46 years, respectively). (In 4 children the ages were not given.)

Among the 11 reported cases with isolated congenital pulmonary insufficiency, 2 patterns were evident. In the smaller group were 4 subjects who died in infancy (2 of these when less than 2 days old). In each, absence of the pulmonary valve was demonstrated at necropsy. In one of these in which thoracic roentgenographic features were reported,[10] the central pulmonary arterial vasculature was normal, while the infundibular part of the right ventricle was prominent. In the larger group were 7 living patients aged 7, 7, 14, 16, 24, 36, and 54 years, respectively, at the time they were reported. Generally, these patients exhibited mild symptoms. Splitting of the second sound was noted in these patients, which suggested that the deformity of the pulmonary valve may perhaps be characterized by the presence of some functional valvular tissue.

SUMMARY

The characteristic clinical features of 2 infants with absence of the pulmonary valve in association with the tetralogy of Fallot included cyanosis and a rough to-and-fro murmur.

Thoracic roentgenograms and roentgenoscopic studies revealed the diagnostic features of very prominent and pulsating infundibulum and major pulmonary arteries. Angiocardiographic studies were most useful in defining the intrinsic anatomic and hemodynamic characteristics of this malformation.

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Vol. 91, No. 3

ROENTGENOGRAPHIC DEMONSTRATION OF ANOMALOUS LEFT CORONARY ARTERY ARISING FROM THE PULMONARY ARTERY*

By ROBERT J. WILDER, M.D., *and* ANTHONY PERLMAN, M.B.B. Ch.
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WITH the continuing improvement in diagnostic and surgical techniques, anomalies of the coronary arteries are now more frequently recognized and corrected. Occasionally, one or both of the coronary arteries may arise from the pulmonary artery instead of the aorta. The first case of anomalous origin of the left coronary artery from the pulmonary artery was reported in 1886 by Brooks.[2] In 1933, Bland, White and Garland[1] reported on 17 cases in which the left coronary artery arose from the pulmonary artery, 2 cases in which the right coronary artery arose from the pulmonary artery, and 2 cases in which both coronary arteries arose from the base of the pulmonary artery. Sabiston *et al.*[4] presented 12 cases in 1960 with a review of the clinical and pathologic findings and emphasized the need for early surgical intervention.

The following case report of an anomalous left coronary artery arising from the pulmonary artery is presented because of the clarity of the roentgenographic findings.

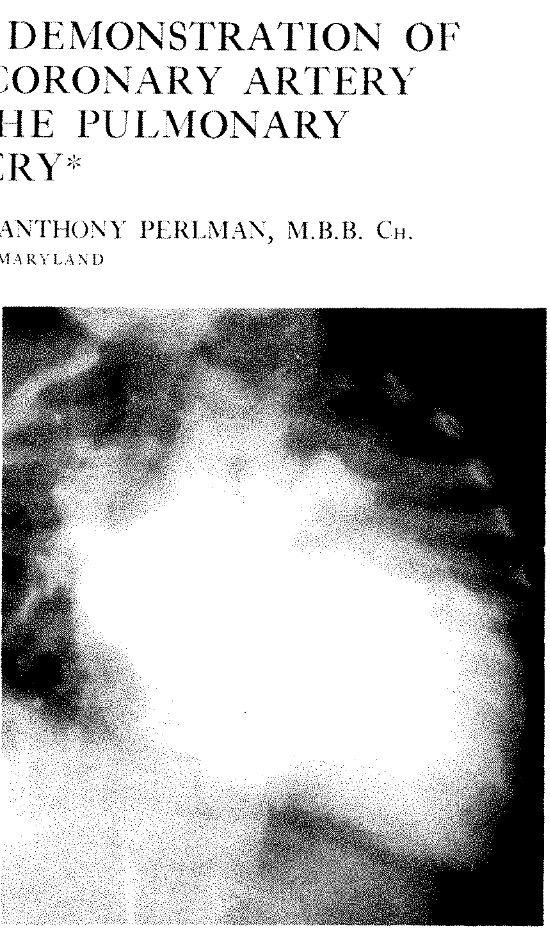

Fig. 1. Right sided angiogram via polyethylene catheter inserted into the inferior vena cava through the saphenous vein. The tremendous size of the left heart chambers is demonstrated as well as the thin left ventricular myocardial wall.

REPORT OF A CASE

Case #321797. This male patient was born on December 30, 1961, following a normal spontaneous delivery. Initial examination revealed an extra digit on the right hand and slight cyanosis. The patient did well and was discharged from the hospital on January 2, 1962.

The child was readmitted April 12, 1962, because of an upper respiratory infection with increasing dyspnea and fever. There was splinting and decreased breath sounds over the left chest. A roentgenogram of the chest revealed a left lower lobe pneumonia and an enlarged heart. The patient responded to antibiotic therapy. An electrocardiogram recorded on April 17, 1962, demonstrated Q-waves in L1, AVL, V4, V5 and V6. There was also slight elevation of the ST segments in V4, V5 and V6, and a nonspecific T-wave abnormality. These findings, suggestive of an anterior myocardial infarction in an infant, are characteristic of anomalous origin of the left coronary artery from the pulmonary artery. Right sided angiography was performed through a polyethylene catheter inserted via the saphenous vein into the inferior vena cava, in order to demonstrate the internal anatomy of the heart. Figure 1 shows the tremendous size of the left heart

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chambers and the thin ventricular myocardial wall.

With the evidence of an enlarged dilated left ventricle, plus the electrocardiographic findings, a diagnosis of anomalous left coronary artery arising from the pulmonary artery was made. Retrograde coronary arteriography was suggested in order to confirm the diagnosis. On June 6, 1962, a No. 5 cardiac catheter was passed retrograde through the femoral artery around the arch of the aorta and positioned just above the aortic valve. Using approximately 7 cc. of 70 per cent urokon, an injection was made with the Gidlund automatic syringe at a pressure of 10 kg. per sq. cm. Roentgenograms (Fig. 2, *A–D*) were obtained on the biplane Schönander apparatus and the first was made after most of the urokon was injected. The anteroposterior and lateral roentgenograms (Fig. 2, *A* and *B*) show the right coronary artery arising from the base of the aorta. It is completely filled with radiopaque medium and there are large collaterals traversing the apex of the heart and joining the left coronary artery which appears to originate from an area that is both anterior and medial to the aorta. In the sequence of roentgenograms that follows, it is possible to observe the opaque medium disappearing from the base of the aorta and the right coronary artery, and draining through the left coronary artery into the structure lying anterior and in the arch of the aorta. In Figure 2, *C* and *D* the pulmonary valves are visible and it becomes obvious that the opaque medium is traveling from the aorta into the right coronary artery through collaterals into the left coronary artery and into the pulmonary artery.

The patient tolerated both angiographic procedures without any ill effects. It was decided to ligate the left coronary artery as it entered the pulmonary artery in order to halt the runoff of blood from the left coronary artery into the pulmonary artery. Pressure in the left coronary artery would be increased and additional blood would be forced into the myocardium. On June 11, 1962, the patient was taken to the operating room and the left coronary artery occluded. At the time of the procedure, the child developed a marked arrythmia and there was a period of inadequate circulation lasting approximately 10 minutes. The ligation was finally accomplished. Postoperatively, the child responded promptly and seemed to be doing well until the second day when he suffered cardiorespiratory arrest. The child responded to tracheostomy, oxygen and closed chest cardiac massage, although it was necessary to maintain him on a positive pressure respirator. A second arrest occurred, however, and although the patient was again resuscitated, he died after a third cardiac arrest on the fifth postoperative day. Postmortem examination revealed bilateral pneumonia with marked secretions in the tracheobronchial tree. The coronary ligature was found around the anterior descending coronary artery. The erroneous ligation of the anterior descending coronary artery, instead of the main left coronary artery, occurred during the second attempt to pass and tighten a ligature around the main left coronary artery without the resulting cardiac arrythmia and inadequate circulation that resulted with the first attempt. There was no sign of myocardial infarction.

DISCUSSION

The diagnosis of anomalous origin of the left coronary artery from the pulmonary artery can be suspected from the history, roentgenogram and electrocardiogram. Positive confirmation of the diagnosis, however, must rest on the visual demonstration of the anomalous origin of the coronary artery by angiographic techniques. The enlarged thin walled myocardium of the left ventricle can be easily visualized on a right sided angiogram. The actual demonstration of a single coronary artery arising from the aorta can only be made by retrograde aortography. The use of retrograde aortography to demonstrate the coronary arteries is well established in the adult and many thousands of such roentgenograms have been recorded. This diagnostic approach to anomalies of the coronary arteries was suggested by diGuglielmo and Guttadauro[3] in 1954.

The difficulties of retrograde coronary aortography in the infant as compared to the adult are only those of size. Great care should be taken by the surgeon in performing the arteriotomy either in the brachial or femoral artery. The catheter used for the procedure should certainly pass through the

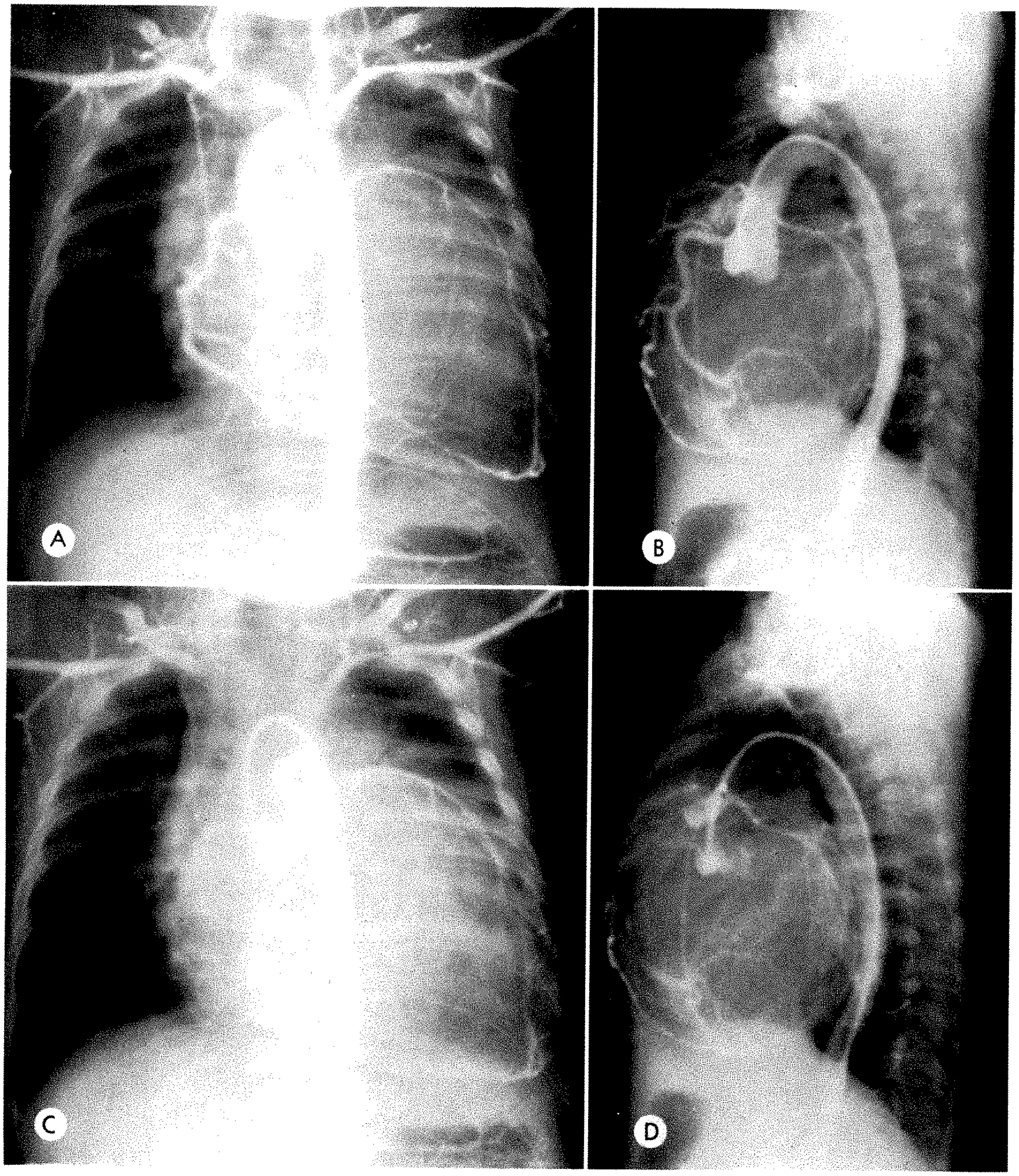

FIG. 2. Retrograde coronary aortography via femoral artery demonstrates the anomalous left coronary artery. (*A*) Anteroposterior and (*B*) lateral aortograms reveal the right coronary artery arising from the base of the aorta. Large collaterals are visible passing over the apex of the heart and joining the left coronary artery which appears to arise from the pulmonary artery lying anterior and medial to the aorta. In subsequent aortograms (*C* and *D*) the opaque medium has disappeared from the base of the aorta and from the right coronary artery and drains from the left coronary artery into the pulmonary artery. The pulmonary valves are visible.

blood vessel lumen easily so as not to damage the wall of the artery or tear the artery at the site of the arteriotomy. The arterial repair requires extremely fine technique. The catheter itself must be positioned just above the aortic valves and the injection made as rapidly as possible. With the use of small catheters necessary in infants, the automatic injector syringe is probably essential in order to get a concentrated bolus of contrast medium into the base of the aorta. It is advisable to have biplane roentgenograms so that conclusive demonstration of the position of the various structures visualized is obtained.

In Figure 2, *A–D*, the flow of the contrast medium from the aorta through the right coronary artery into the left coronary artery and into the pulmonary artery is obvious. Such evidence supports the postulate of Brooks[2] that there is a retrograde flow of blood through the anomalous coronary artery. The low pressure in the pulmonary artery allows this retrograde flow to occur resulting in a low pressure in the anomalous coronary artery and thereby depriving the myocardium of adequate nutrition. In this case, the contrast medium was injected into the base of the aorta. It appeared in the pulmonary artery. Since there were no other abnormalities, this could have occurred only by retrograde flow from the right coronary artery through the left coronary artery and finally into the pulmonary artery. The use of retrograde aortography to demonstrate an anomalous origin of the left coronary artery from the pulmonary artery confirmed the diagnosis and provided further evidence of the retrograde flow of blood in the anomalous coronary artery.

SUMMARY

A case report is presented of an infant in whom the presence of an anomalous left coronary artery arising from the pulmonary artery was confirmed by retrograde coronary aortography. Angiograms showed the anomaly and demonstrated the retrograde flow of blood from the left coronary artery into the pulmonary artery.

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ABERRANT LEFT CORONARY ARTERY

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ABERRANT left coronary artery is a rare congenital anomaly characterized by origin of the left coronary artery from the root of the pulmonary artery. Since first described by Abrikosoff[1] in 1911, and clarified by Bland, White, and Garland[4] in 1933, approximately 75 cases have been reported. The condition is usually rapidly fatal, but prompt recognition offers the prospect of surgical amelioration. Several excellent reviews have appeared recently[5,7,9,13] in which emphasis has been placed on the clinical and pathophysiologic features. Because angiocardiography may play a decisive role in diagnosis and since the angiocardiographic features have not been thoroughly described, our experience with 5 cases is presented, stressing these features and the differentiation from the more common condition of subendocardial fibroelastosis.

CLINICAL ASPECTS

About 80 per cent of reported cases of aberrant left coronary artery are of the so-called infantile type, where severe cardiac symptoms appear very early in life—usually from the neonatal period up to the age of 3–4 months. Symptoms may be failure to thrive or dyspnea, but frequently the child will behave as if in pain during feedings, suggesting angina pectoris. Physical examination will reveal marked cardiomegaly, signs of heart failure, and absent or inconspicuous heart murmurs. The electrocardiogram usually, but not always, shows signs of left ventricular infarction and hypertrophy.[9] Routine cardiac roentgenograms show marked cardiomegaly, usually recognizable as being predominantly left ventricular in origin, but the appearance is not specific. The left ventricle may reach aneurysmal proportions (12 out of 45 cases reviewed by Cohen and Siew[5]) with associated compression atelectases of portions of the left lung. Fluoroscopy will show poor cardiac pulsations. Death usually occurs within the first 6 months.

Fifteen to 20 per cent of cases of aberrant coronary artery are of the adult type, wherein the patients are relatively asymptomatic and may live to beyond the age of 60. Some, however, have angina, and many have been prone to sudden death.[7] Physical examination usually reveals a machinery-like continuous cardiac murmur. There is no general agreement as to the cause of this murmur, but it is probably attributable to the large collateral flow from the right coronary artery.[7] The electrocardiogram shows moderate left ventricular hypertrophy, and may, as in our case, show left ventricular infarction. Plain cardiac roentgenograms show mild to moderate left ventricular enlargement.

It seems appropriate to briefly mention aberrant *right* coronary artery. This is even less common than aberrant left coronary artery, and mention of only 6 cases has been found in the literature.[5,8] In all cases the lesion has been an incidental finding at autopsy, and apparently has been of little or no clinical significance.

PATHOLOGIC PHYSIOLOGY

Since the left coronary artery originates from the pulmonary artery, at the time of birth it supplies portions of the myocardium with venous blood at pulmonary pressures. During the neonatal period the anomaly may not be clinically apparent; the relatively high pulmonary artery pressure of this period, probably in association with augmented collateral flow from the normal right coronary artery, is apparently adequate to supply basic myocardial needs. However, with time, pulmonary artery pressures adjust to lower levels. Because of the extensive collateral flow supplying blood at systemic pressures, the aberrant coronary artery then begins to conduct blood in a retrograde manner, *i.e.*, back toward the pulmonary artery.[13] Thus, not only does the left coronary artery fail to adequately nurture myocardium, but it actually drains away much of the collateral blood supplied by the right coronary artery. Of greatest physiologic consequence is the low level of pressure in the aberrant coronary artery, which cannot be maintained significantly above pulmonary artery pressure.[13] Myocardial anoxia and infarction usually supervene. When left ventricular failure develops with consequent fall of systemic and elevation of pulmonary pressures, the flow in the aberrant artery may once again become "forward."

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PATHOLOGIC ANATOMY

Gross examination of the heart generally reveals extensive left ventricular infarction. This tends to be of greatest severity in areas most remote from sources of collateral supply, that is, in the anterior portion of the interventricular septum, the anterior and lateral portions of the left ventricle, and in the papillary muscles. Although Keith[9] states that the left ventricular wall may be of normal thickness, there is usually extreme thinning and fibrosis of the wall at the apex. This was true in all our cases. The base and posterior wall of the left ventricle may be hypertrophied. Histologically, myocardial infarctions will be found in various stages of development and repair. Dystrophic calcification occurs in necrotic myocardium in about 50 per cent of cases,[9] but has never been reported roentgenographically. Some degree of left ventricular endocardial fibroelastosis is invariably present.[9]

Angiocardiographic observations have received little attention in the literature. Sabiston *et al.*[14] refer to massive enlargement of the left ventricle and left atrium, with prolonged circulation time. The left ventricular wall has been described as "thin"[14] or "relatively thin."[9] On intravenous angiocardiograms the aberrant coronary artery was visualized in none of 4 cases reported by Sabiston *et al.* and in 1 of 5 cases reported by Keith. Aortograms will show failure of direct opacification of the left coronary artery from the aorta. In an adult type case, Agustsson *et al.*[2] demonstrated angiographically the extensive collateral circulation from the dilated, but otherwise normal, right coronary artery which opacified the aberrant left coronary artery, and in turn, the pulmonary artery.

METHOD AND MATERIALS

In an effort to more fully evaluate the angiocardiographic features of aberrant coronary artery and to establish differential features from endocardial fibroelastosis, 5 cases of aberrant left coronary artery and 11 cases of endocardial fibroelastosis were reviewed. The cases of aberrant coronary artery are briefly presented below. Salient clinical features of these cases as well as those of endocardial fibroelastosis are summarized in Table I. All cases were studied angiographically. Except for Case II, these studies were performed on the biplane Elema serial changer, with a target film distance of 90 cm. The magnification factor was approximately 1.25 in anteroposterior projections and 1.35 in lateral projections. Films were exposed at the rate of 6 per second or 2 per second, but in all cases exposures were fast enough to show the left-sided chambers in varying phases of the cardiac cycle. A simultaneous electrocardiogram was obtained, which indicated the time of each roentgenographic exposure. The comparative angiographic features are shown in Table II. The thickness of the left ventricular wall was measured directly from the roentgenograms without correction for magnification. Calculation of left ventricular volumes was according to the "three measured length" method of Dodge *et al.*[6] Calculation of left atrial volumes was according to Arvidsson.[3] Figures for normal mensuration are based upon analyses of a limited number of normal cases and should be considered only approximate.

Table I

SUMMARY OF NONANGIOCARDIOGRAPHIC FEATURES

Diagnosis	Case	Onset Symptoms	Murmurs	Electrocardiographic Findings	Plain Roentgenograms	Course
Aberrant coronary artery	J.H.	Respiratory distress 3½ mo.	Soft systolic LSB	Anterolateral infarction	Cardiomegaly, aneurysmal LVE	Death during surgery at age 6 mo.
	L.H.	Failure to thrive from age 6 wk.	None	Posterolateral infarction	Cardiomegaly, LVE	Death at age 6 mo.
	D.M.	Failure to thrive from age 2 mo.	None	LVH, T-wave changes	Nonspecific cardiomegaly	Death at age 5½ mo.
	J.M.	Weak cry from age 2 wk.	None	Anterolateral infarction	Cardiomegaly, RLL atelectasis	Death at age 6 mo.
	D.V.	None	Continuous systolic	Anterolateral infarction	Slight LVE	Living and well at age 11 yr.
Endocardial fibroelastosis	D.D.	Dyspnea at age 4 mo.	Faint apical systolic	LVH and myocardial changes	Marked LVE and LAE	Living and well at age 5 yr.
	V.D.	Dyspnea at age 4 mo.	Faint apical systolic	LVH and myocardial changes	LVE and LAE	Living and well at age 4 yr.
	R.H.	Repeated URI from age 6 wk.	Faint apical systolic	LVH	Generalized cardiomegaly	Living and well at age 4 yr., murmur gone
	M.L.	Dyspnea at age 12 mo.	Systolic, 3rd intercostal space, LSB	Normal	Mild cardiomegaly, LVE	Living and well at age 2½ yr.
	K.M.	Failure to thrive from age 5 da.	None	RVH, incomplete right bundle-branch block	Cardiomegaly, pulmonary congestion	Living with symptoms at age 8 mo.
	M.M.	Anorexia from age 3 mo.	None	LVH, myocardial changes	Cardiomegaly, LVE	Death at age 24 mo., autopsy confirmation
	K.R.	Dyspnea from age 7 wk.	Faint apical systolic	LVH, myocardial changes	Cardiomegaly, LVE, LAE	Death at age 11 mo., autopsy confirmation
	C.S.	Anorexia from age 4 mo.	Faint apical systolic	LVH, myocardial changes	Cardiomegaly, atelectasis LUL	Death at age 18 mo., no autopsy
	T.S.	Syncopal attacks from age 2 mo.	Faint apical systolic	Myocardial changes	Cardiomegaly, LVE, congestion	Death at age 5 mo., autopsy confirmation
	R.W.	URI from birth	Faint apical systolic	Suggested generalized cardiomegaly	Huge LV	Living, fairly well at age 3½ yr.
	C.W.	Dyspnea at age 11 mo.	Faint apical systolic	LVH	Marked LVE, mild LAE	Death at age 14 mo., autopsy confirmation

Key: URI=Upper respiratory infection.
LSB=Left sternal border.
LVH=Left ventricular hypertrophy.
RVH=Right ventricular hypertrophy.
LVE=Left ventricular enlargement.
LAE=Left atrial enlargement.
RLL=Right lower lobe.
LUL=Left upper lobe.

REPORT OF CASES

Case 1. J.H., a 4 month old white male, was well until the age of 3½ months when he developed cough and vomiting, irritability and respiratory distress. The patient was referred to The University of Michigan Medical Center, where physical examination revealed cardiomegaly and a soft systolic murmur at the left sternal border. An electrocardiogram suggested anterolateral myocardial infarction. Chest roentgenograms showed marked cardiomegaly (Fig. 1, *A* and *B*), predominantly left ventricular. Intravenous angiocardiograms showed an extremely large, poorly pulsating left ventricle, with a thin lateral wall that did not thicken with systole (Fig. 2, *A* and *B*). There was no evidence of opacification of the coronary artery from the pulmonary artery. Two days later retrograde aortography was performed, showing immediate opacification of the right coronary artery from the aorta (Fig. 3, *A–D*). Within ½ second, the left coronary artery was opacified via collateral conus, interventricular, and posterior ventricular branches. The origin of the left coronary artery was seen to be in the region of the pulmonary artery, but the pulmonary artery was not opacified. At 3 seconds there was noticeably increased staining of portions of the left ventricular wall, especially laterally, where the myocardium appeared extremely thin (Fig. 4*A*). One week later the patient underwent an attempted coronary artery transplant. The left coronary artery, with a surrounding cuff, was removed

TABLE II

ANGIOCARDIOGRAPHIC FEATURES

Diagnosis	Case	Age	Wt. (lb.)	Left Ventricular Systole			Left Ventricular Diastole			Left Atrial Volume		Enlargement of		Per Cent Contraction		Coronary Flow	Injection Site
				Lateral wall (mm.)	Posterior wall (mm.)	Volume (cc.)	Lateral wall (mm.)	Posterior wall (mm.)	Volume (cc.)	Systolic (cc.)	Diastolic (cc.)	Left ventricle	Left atrium	Left ventricle	Left atrium		
Aberrant coronary artery	J.H. 001265	4 mo.	16	—	8	66	—	7	76	5.5	11	3x	3x	13	50	Retrograde	Intravenously and aorta
	L.H. 858653	6 mo.	10	2½	—	—	2½	—	— (single plane study)	—	—	~3x	—	—	—	Forward	Pulmonary artery
	D.M. 876802	3 mo.	9	—	3–4	55	—	2–3	70	11	15	4.5	3	20	30	Forward	Intravenously
	J.M. 935361	3 mo.	11	—	—	66	—	—	66	3.5	7.2	4	1.5	0	50	Retrograde (inferred)	Intravenously
	D.V. 861733	9 yr.	55	5–10	10	~35	8–17	12	124	—	—	~1.5	—	72	—	Retrograde	Left ventricle
Normal*		6 mo.	16	>10	>10	~4	5	5	25	3	8	1	1	85	66	Coronaries seen	
Endocardial fibro-elastosis	D.D. 937141	4 yr.	40	9	—	~150	9	—	150	21	28	2.5	2	~0	23	No	Pulmonary artery
	V.D. 914537	5 mo.	13	—	12	41	—	9	51	9	17	2	2	20	44	No	Pulmonary artery
	R.H. 885222	11 mo.	22	10	17	93	4–6	9	102	23	35	2.5	2	9	34	No	Intravenously
	M.L. 984857	12 mo.	16	6	7–10	56	5.5	6–9	66	—	—	2	—	15	—	No	Left ventricle
	K.M. 008367	7 wk.	8	5.5	4	33	4	3.5	45	—	—	3	—	27	—	Yes	Left ventricle
	M.M. 948375	5 mo.	16	5.5	—	108	5	—	115	—	—	4.5	—	6	—	Yes	Left ventricle
	K.R. 920098	6 mo.	12	5–7	—	72	—	—	92	16.5	25	4.5	3	22	36	No	Intravenously
	C.S. 995068	6 mo.	13	—	—	62	—	9	89	6	9.5	4	1	30	37	No	Pulmonary artery
	T.S. 894945	4 mo.	9½	12	11	21	6	6	32	6	10.5	2	2	34	40	No	Intravenously
	R.W. 899371	9 mo.	14	10	—	41	5–8	—	59	5.5	14	2	2	30	61	Yes	Pulmonary artery
	C.W. 900389	12 mo.	18	7	8	134	4	—	143	10	25	3	2	6	60	No	Pulmonary artery

* Based on a limited number of normal studies from this institution.

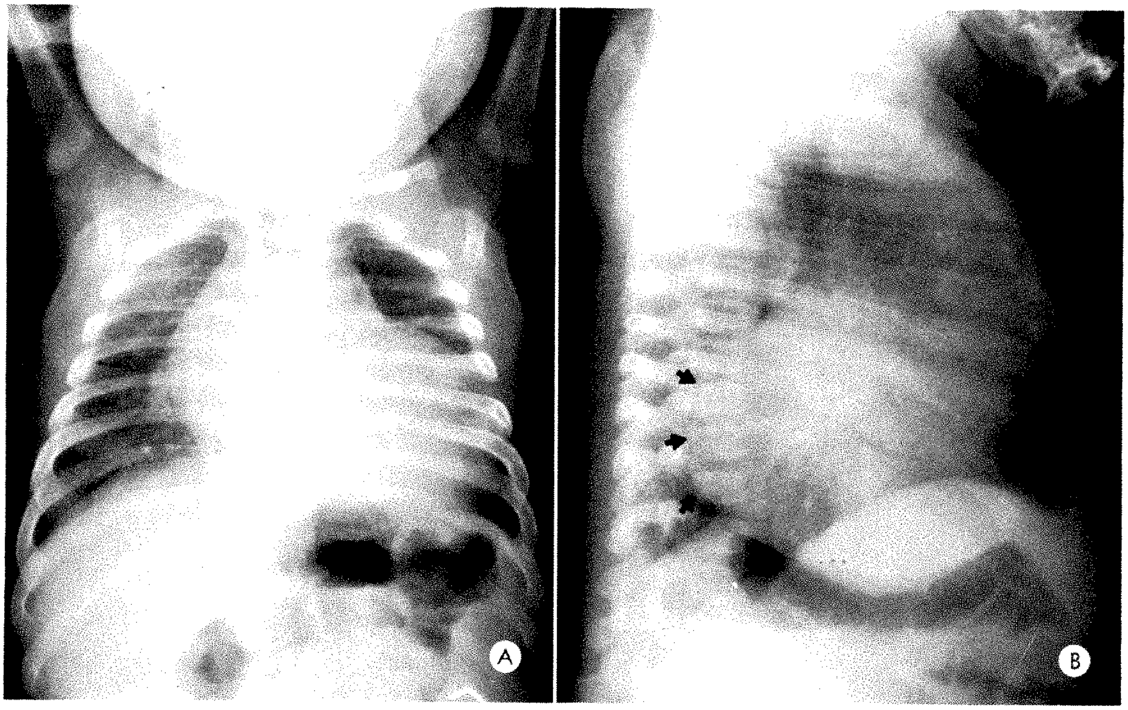

FIG. 1. Case 1 (J.H. #001265). (*A*) Posteroanterior and (*B*) lateral chest roentgenograms show moderate cardiomegaly. The marked posterior prominence of the cardiac silhouette (arrows), without corresponding retrosternal fullness, indicates marked left ventricular enlargement. There is mild pulmonary congestion

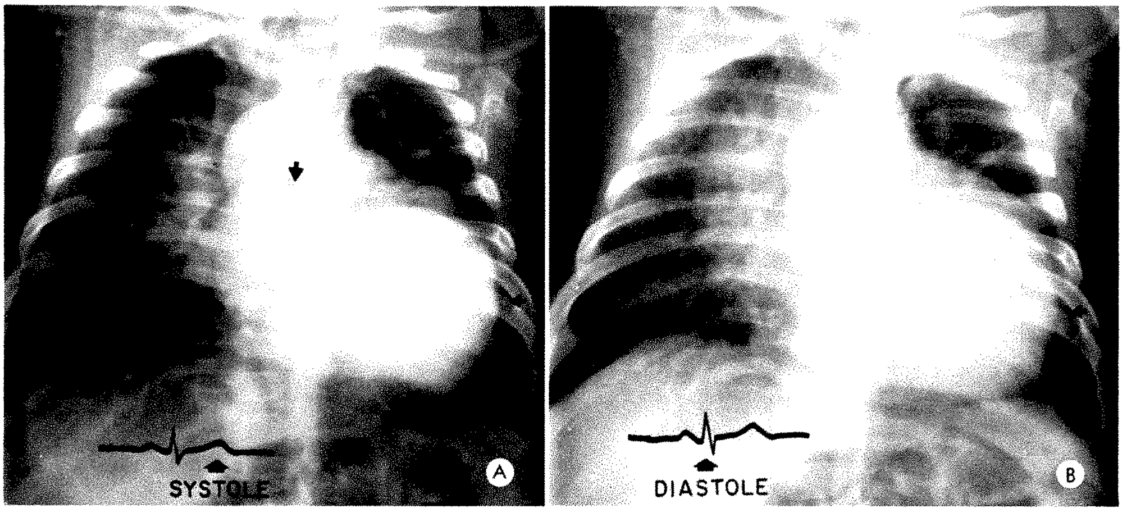

FIG. 2. Case 1. (*A* and *B*) Intravenous angiocardiograms. Note marked enlargement of the left ventricle with barely appreciable systolic contractions. Note the thin lateral wall of the left ventricle (←), with no appreciable systolic thickening. On lateral views (not shown) the posterior wall was of normal thickness in diastole (7 mm.) and thickened slightly with systole. A coronary artery is visible (↓ slightly retouched), subsequently shown to represent the right coronary artery.

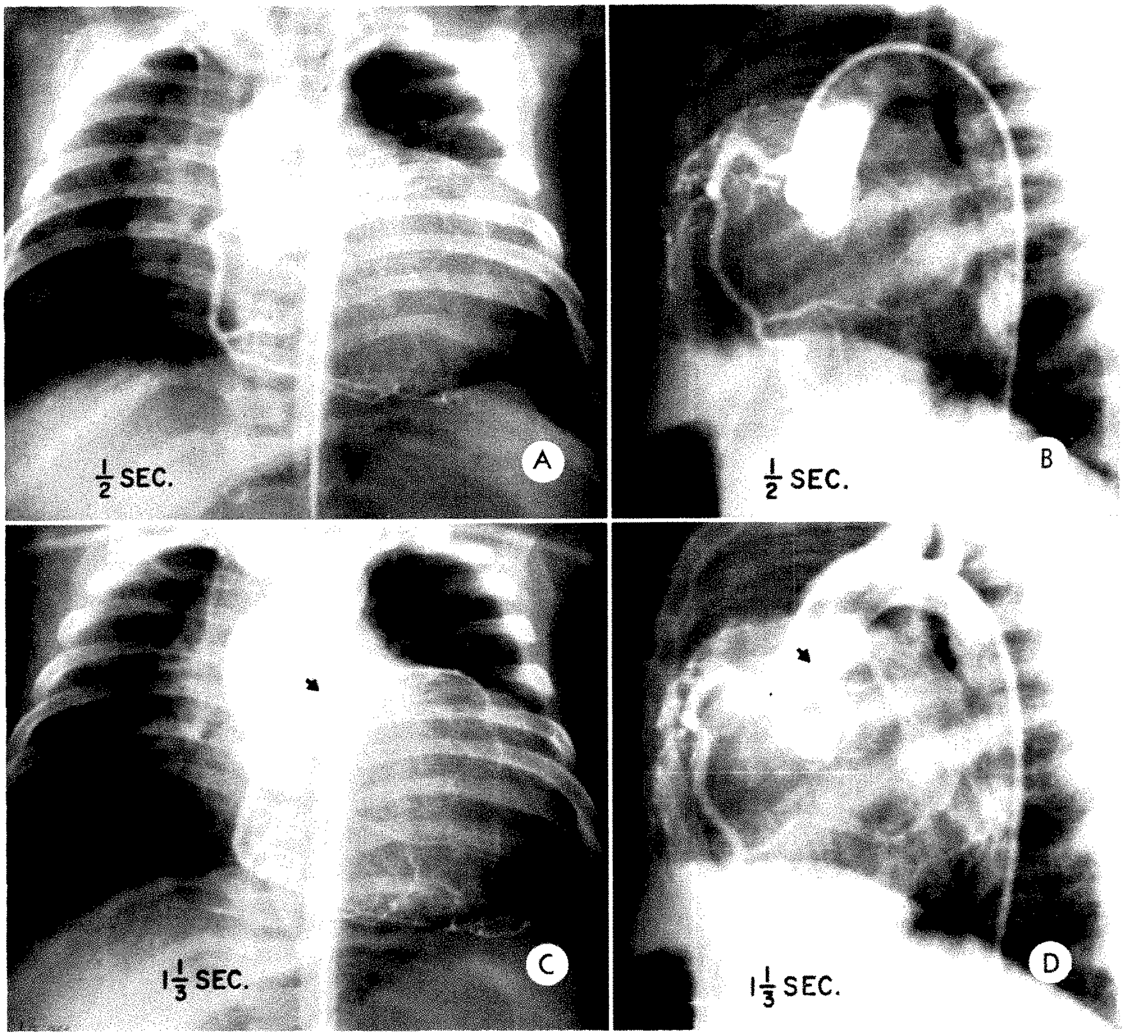

FIG. 3. Case I. (*A*, *B*, *C* and *D*) Coronary arteriograms. Only the moderately dilated right coronary artery arises directly from the aorta. Less than a second later, the left coronary artery is opacified via prominent conus, posterior ventricular, and interventricular collaterals. Note that its origin (↘) is in the region of the posterior aspect of the pulmonary artery.

from the pulmonary artery, at which time considerable oxygenated blood was noted issuing from its ostium. The artery was then successfully anastomosed to the aorta. Unfortunately, adequate left ventricular contractions could not be maintained, and the child succumbed a few hours postoperatively. At autopsy, the heart weighed 100 gm. The left coronary artery originated from the posterior aspect of the root of the pulmonary artery. Extensive infarction, both recent and old, was present over much of the left ventricle, especially involving the lateral wall, floor, and papillary muscles. Posteriorly, the left ventricular wall was 9 mm. thick. Laterally and toward the apex, it thinned to 2 mm. The papillary muscles grossly contained calcium. The surgical anastomosis of the left coronary artery was patent. Histologic examination of regions noted to have increased staining on angiocardiograms showed infarcts of several weeks in which extensive fibro-angiomatous transformation was evident (Fig. 4*B*).

CASE II. L.H., a 6 month old white female, had failed to gain weight satisfactorily since the age of 6 weeks. Progressive dyspnea developed at the age of 3 months. Examination at The University of Michigan Medical Center re-

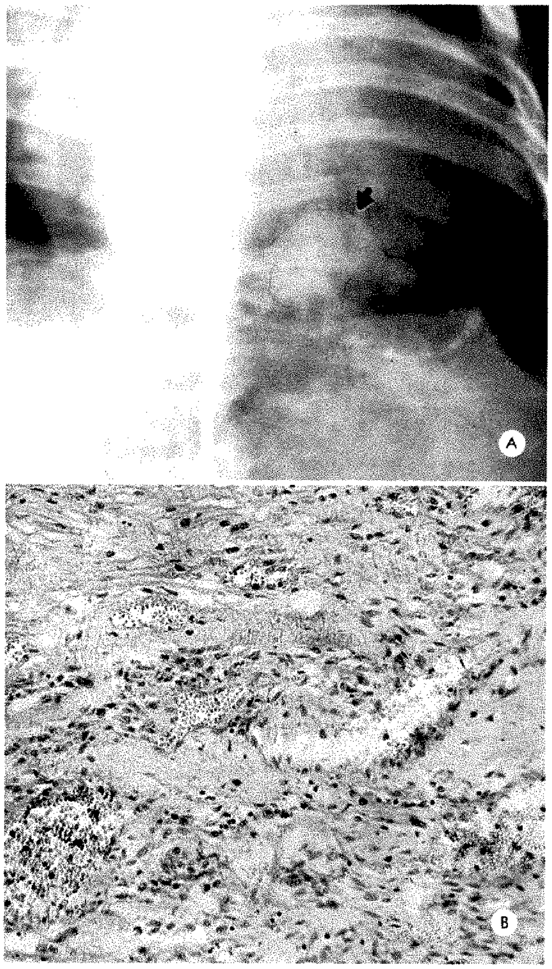

Fig. 4. Case i. (*A*) Three seconds after the injection, increased staining of the myocardium along the floor and lateral wall of the left ventricle, representing areas of healing infarction (↙ ↘) is seen (retouched). (*B*) Photomicrograph of a section taken from the lateral wall of the left ventricle. Note complete replacement of myocardial fibers by fibrous and angiomatous tissue.

vealed a tachypneic female with circumoral cyanosis when crying. The heart was enlarged, without murmurs being present. An electrocardiogram suggested fresh posterolateral myocardial infarction. Plain roentgenograms showed marked cardiomegaly, predominantly left ventricular. Cardiac catheterization revealed a pulmonary artery oxygen saturation of 52 to 56 per cent with mean pulmonary artery pressures of 50 mm. of mercury. A selective pulmonary artery angiocardiogram showed opacification of the left coronary artery from the pulmonary artery (Fig. 5*A*). The left ventricle was markedly enlarged with poor contractions and had a very thin lateral wall which did not thicken with systole (Fig. 5*B*). Surgical transplantation of the coronary artery was planned, but ventricular fibrillation developed during induction of anesthesia, and the child died.

At autopsy, the left ventricle was very large, with thinning of the left ventricular wall to 1 mm. at the apex and in the anterior portion of the interventricular septum. Posteriorly the left ventricular wall was approximately 10 mm. thick. Microscopically, extensive old left ventricular infarction was present. The left coronary artery originated from the posterior aspect of the pulmonary artery.

Case iii. D.M., a 3 month old female, was admitted for study because of failure to gain weight since the age of 2 months. Physical examination revealed marked cardiomegaly and no murmurs. The electrocardiogram suggested left ventricular hypertrophy (without evidence of infarction).

Chest roentgenograms showed marked cardiomegaly and atelectasis of the left lower lobe. Intravenous angiocardiograms showed opacification of an aberrant left coronary artery from the pulmonary artery (Fig. 6, *A* and *B*). The left ventricle was markedly enlarged, with a thin unchanging lateral wall. The child was sent home on medical management and died at the age of 5½ months. Autopsy revealed an aberrant left coronary artery, with marked enlargement of the left ventricle. The left ventricular wall was 1 cm. thick near the base and 2 mm. thick near the apex.

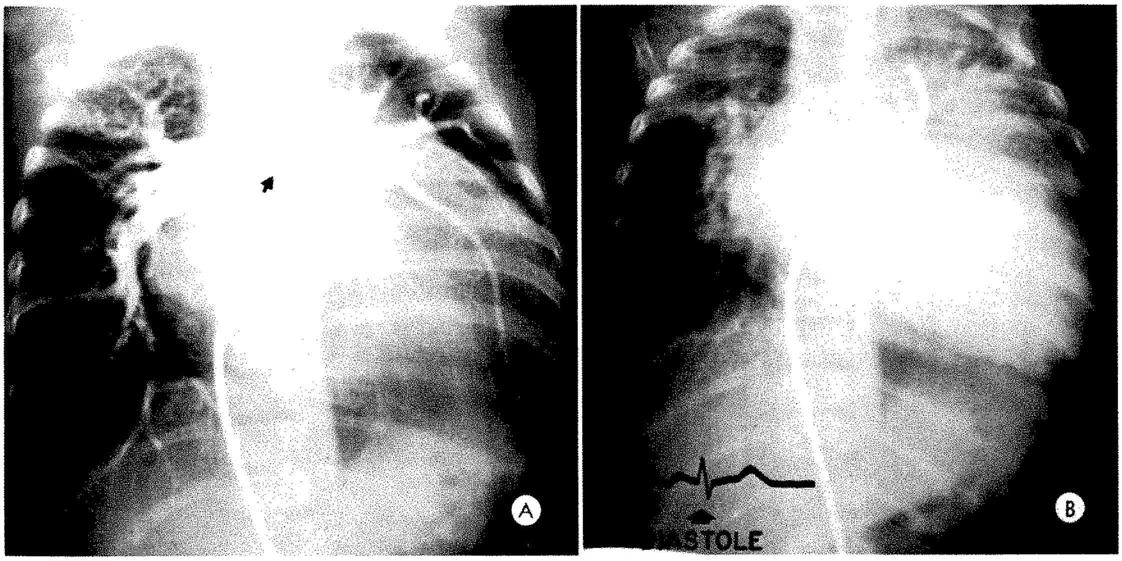

Fig. 5. Case II (L.H. #858653). (*A*) Selective pulmonary arteriogram demonstrates opacification of the left coronary artery (↗) from the pulmonary artery. In this case, the low systemic pressures, in combination with elevated pulmonary artery pressures (50 mm. Hg mean), presumably explains the forward flow in the aberrant coronary artery. (*B*) Later arteriogram shows a markedly, dilated, poorly pulsating left ventricle, with the lateral wall too thin to measure. There was no appreciable thickening of the lateral wall with systole.

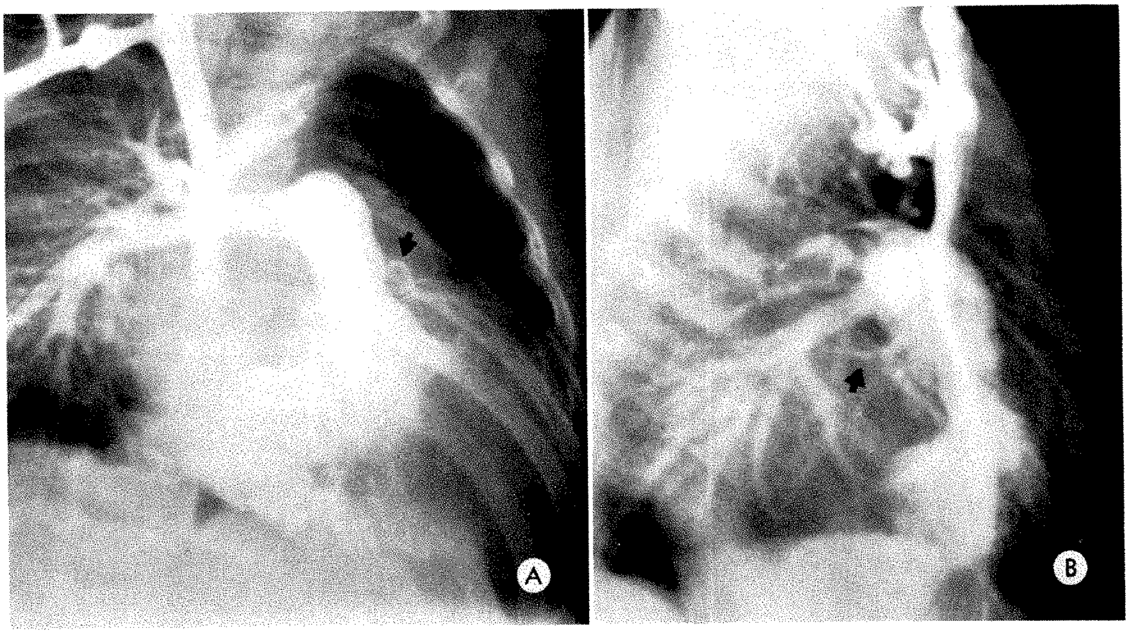

Fig. 6. Case III (D.M. #876802). (*A* and *B*) Angiocardiograms clearly showing the aberrant left coronary artery originating from the posterior aspect of the pulmonary artery (arrows). Later roentgenograms (not shown) revealed the typical, dilated, nonpulsatile left ventricle with a thin unchanging lateral wall.

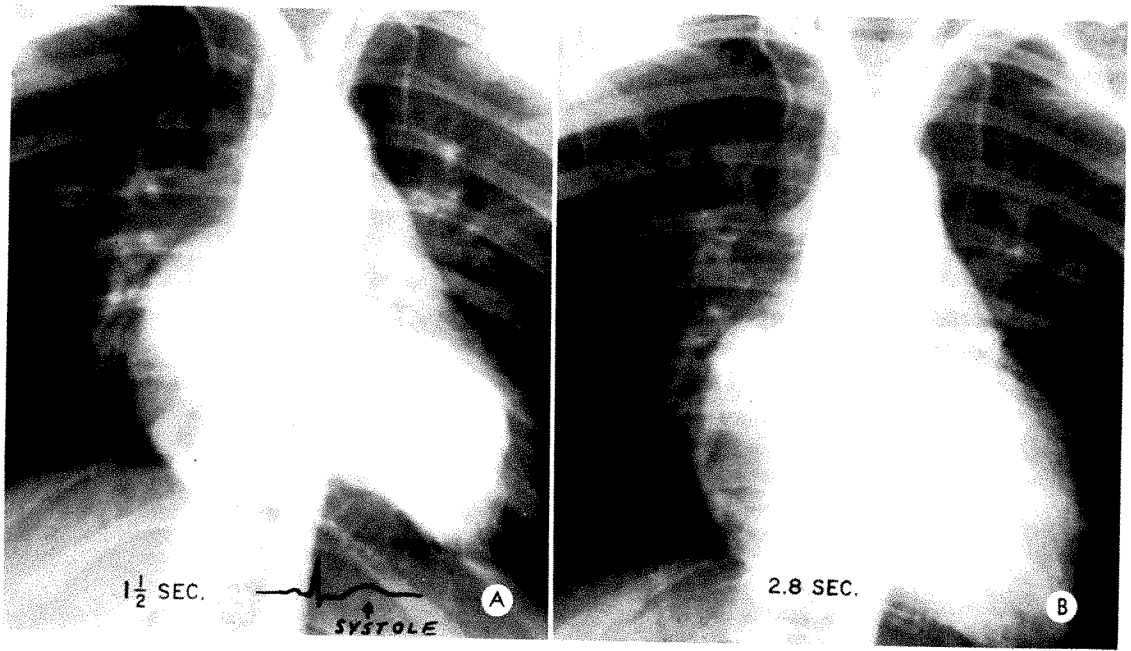

FIG. 7. Case v. (D.V. #861733). (*A* and *B*) Selective left ventricular angiocardiograms with the adult type aberrant left coronary artery. At 1½ seconds a dilated right coronary artery opacifies directly from the aorta. One second later, the left coronary artery (←) is opacified via collateral vessels. At 3 seconds (roentgenogram not shown), there was faint opacification of the pulmonary artery, proving confluence of the left coronary artery with the pulmonary artery. Note the thinning of lateral left ventricular wall (↙), indicating an area of myocardial infarction. Note incomplete end-systolic contraction of the left ventricle. There is minimal mitral insufficiency.

CASE IV. J.M., a 3 month old male, was well until 2 weeks of age when his mother noted the onset of a weak cry and temporary cyanosis. Similar episodes occurred repeatedly, and the patient was referred to The University of Michigan Medical Center for evaluation. Physical examination revealed signs of right pneumonitis, cardiomegaly, and heart failure. There were no significant cardiac murmurs. The electrocardiogram suggested anterolateral myocardial infarction. Plain cardiac roentgenograms showed cardiomegaly, predominantly left ventricular, atelectasis of the right lower lobe, and pneumonitis of the right upper lobe. An intravenous angiocardiogram showed a markedly enlarged, poorly contractile, thin-walled left ventricle, with no appreciable systolic-diastolic change in thickness of the lateral or posterior walls. The patient was referred to home care and expired at the age of 6 months.

Autopsy revealed an aberrant left coronary artery, with marked left ventricular dilatation. The left ventricular wall measured 1 mm. in thickness at the apex and in the anterior portion of the interventricular septum. Microscopically, there was extensive infarction in the anterolateral portion of the left ventricle.

CASE V. D.V., a 9 year old female, was in apparently good health despite a known heart murmur since the age of 4. The patient was referred to The University of Michigan Medical Center for further evaluation. Physical examination revealed evidence of mild left ventricular hypertrophy and enlargement. There was a holosystolic Grade IV murmur and thrill at the apex. A continuous murmur was also noted in the 2nd and 3rd interspaces at the left sternal border. Chest roentgenograms suggested moderate left atrial and slight left ventricular enlargement. The electrocardiogram suggested an old anteroseptal infarction. Selective left ventricular angiocardiograms (Fig. 7, *A* and *B*) showed a mildly enlarged left ventricle which contracted incompletely. One area along the upper lateral wall, thought to represent an old infarction, was moderately thinned and showed only minimal increase in thickness with systole. The remaining left ventricular wall seemed slightly thickened. A large tortuous right cor-

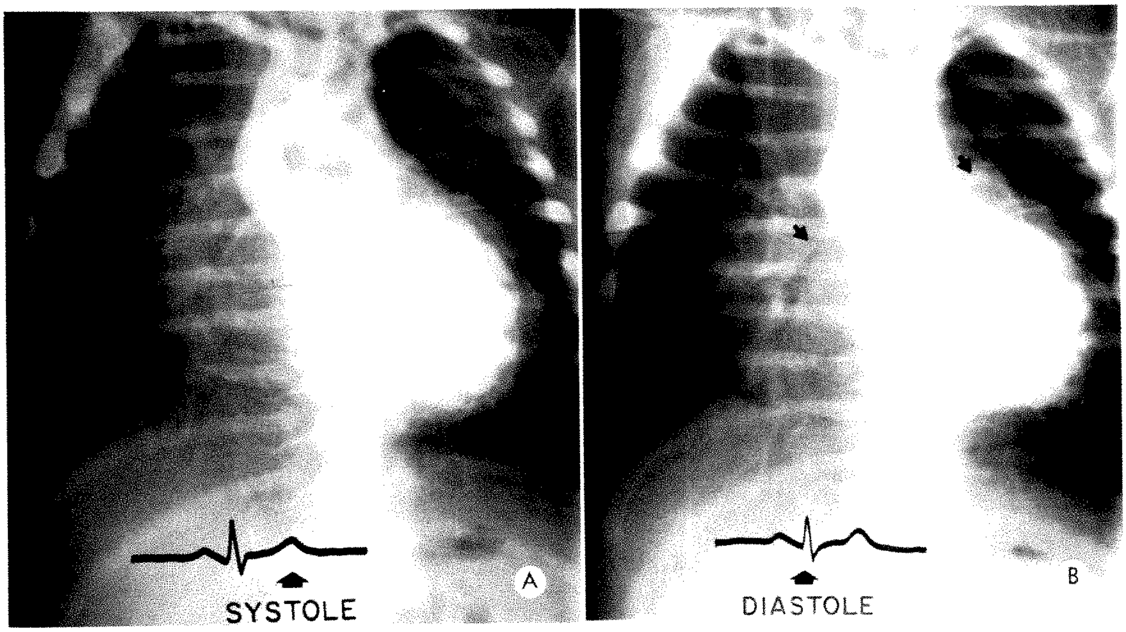

Fig. 8. Case vi (K.M. #008367). (*A* and *B*) This patient was a 7 week old female who failed to thrive from the age of 5 days. A male sibling had died as an infant, and autopsy had revealed endocardial fibroelastosis. Plain roentgenograms showed generalized cardiomegaly, predominantly left ventricular in origin, and mild pulmonary congestion. The electrocardiogram suggested left ventricular hypertrophy with myocardial changes. Selective angiocardiograms reveal a moderately enlarged, poorly pulsating left ventricle. Lateral wall is of normal thickness, and thickens slightly, but definitely, with systole. Coronary arteries (↘ ↘) appear normal.

onary artery originated normally from the aorta, but the left coronary artery was opacified after a ½ second delay via collateral branches. Faint opacification of the pulmonary artery then became evident, and the diagnosis of aberrant left coronary artery was established. Surgical correction was suggested, but refused by the patient's mother. The child remains relatively asymptomatic at the age of 11 years.

DISCUSSION

In Table i pertinent nonangiographic data of our case material are summarized. It may be seen that all infantile type cases of aberrant left coronary artery developed symptoms before the age of 4 months and had no significant cardiac murmurs. Plain roentgenograms showed marked cardiomegaly in all cases, which on oblique views seemed to be predominantly left ventricular in origin. In 1 case, the left ventricle could be considered of aneurysmal proportions on plain roentgenograms. The electrocardiogram was very helpful, suggesting myocardial infarction in 4 of 5 cases (including the adult type case); yet, in 1 case (Case iii) the electrocardiogram indicated only left ventricular hypertrophy. On the other hand, it must be borne in mind that myocardial infarctions may occur in infancy from causes other than aberrant coronary artery.[15] Therefore, it is apparent that a diagnosis of aberrant left coronary artery cannot be made or excluded with certainty on clinical data alone, and angiocardiography offers a further invaluable diagnostic adjunct.

Table ii shows a summary of the pertinent angiographic observations on the previously cited material. In 4 cases the coronary arteries were visualized, and in 3 of these the angiocardiogram conclusively demonstrated a confluence between the pulmonary artery and the left coronary artery. In Cases ii and iii blood flowed "forward" from the pulmonary artery into the coronary artery. In Case v, retrograde flow in the aberrant coronary artery resulted in secondary opacification of the pulmonary artery. In Case I, the origin of the left coronary artery was seen to be in the region of the pulmonary artery, implying, but not conclusively proving, retrograde flow into the pulmonary artery. In Case IV, the direction of flow was also presumably retrograde, as inferred from the lack of left coronary visualization on the intravenous study. It must be emphasized, however, that retrograde opacification of the left coronary artery by collateral circulation *without* secondary opacification of the pulmonary artery is not pathognomonic of aberrant left coronary artery; a left coronary artery obstructed at its origin may also opacify via collateral vessels from the right coronary artery.[11]

Another striking feature, present in every case, was thinning of the lateral left ventricular wall. This was too thin to measure in 3 cases and about 2½ mm. in 1 case. In the single case of the adult type, the thinning seemed to be localized to a small area near the base, apparently a site of infarction. Of the 4 infantile cases, lateral views were available in 3. In 2 of these, the posterior left ventricular wall was thinned, while in Case I the posterior wall was thickened. It seems likely that the predilection for involvement of the lateral left ventricular wall reflects the greater tendency for ischemia and infarction of the myocardium situated farthest from the collateral supply.

Of particular importance is the demonstration of unchanging thickness of these involved portions of myocardium between systole and diastole, strongly suggesting infarction. Although one might expect actual systolic thinning of the infarcted areas, this was not observed in any case, possibly because the involved areas were already too thin to measure accurately. Likewise, there was no evidence of paradoxical pulsation. As can be seen from Table II, left ventricular contraction was very poor, with consequent marked prolongation of the time required for contrast medium to clear from the left ventricle (6 to 7 seconds in most cases).

DIFFERENTIAL DIAGNOSIS

Several entities may closely mimic aberrant left coronary artery, both clinically and angiographically, including endocardial fibroelastosis, myocarditis, von Gierke's disease of the heart, and medial necrosis of a coronary artery. Because of its relative frequency, endocardial fibroelastosis is the chief problem in differential diagnosis (Fig. 8, *A* and *B*). Since aberrant left coronary artery is amenable to surgical correction, it is of more than academic interest to establish this differentiation.

A study of Table I reveals certain clinical features which may be of help in differentiating aberrant coronary artery from endocardial fibroelastosis. The age of onset of symptoms may be of significance, for, although both entities may become symptomatic by the age of 4 to 6 months, endocardial fibroelastosis is much more likely to be found in a child presenting beyond this age. The electrocardiogram showed myocardial infarction in 4 of 5 cases of aberrant coronary artery, and in none of the cases of endocardial fibroelastosis. Nevertheless, the lack of electrocardiographic evidence of infarction in Case III emphasizes the limitations of differentiation by this method alone.

Table II shows the differential value ot certain angiographic features. If the coronary arteries are well visualized, either on right or left-sided injections, the differentiation becomes obvious. The greatest problem arises in those cases studied by right-sided injection only, where the coronary arteries are not seen. In both entities a very large, poorly contractile left ventricle will be evident. However, in aberrant left coronary artery, the lateral left ventricular wall is markedly thinned and remains thinned during systole. On the other hand, in cases of endocardial fibroelastosis, the lateral wall may be thinned, normal, or thickened, but it will show some increase in thickness with systole. Observation of left ventricular wall thickness and its cyclic behavior would have enabled differentiation in all our cases but one. In this particular case (C. S.) the left ventricular wall thickness could not be estimated because of poor aeration of adjacent lung.

In Table III pertinent differentiating features are summarized.

Many other features were compared and found to be of little or no help in differentiation, including: compression of right ventricle by enlarged left ventricle, size and degree of emptying of the left atrium or ventricle, configuration and smoothness of the left ventricle, and time required for contrast material to clear from the left ventricle.

As previously mentioned, numerous other entities may be associated with dilated and poorly contractile left ventricles, but in all these, the left ventricular wall would be expected to appear thick, or at least to thicken during systole. Most difficult to differentiate would be those infants with occlusive disease of the left coronary artery. Failure to demonstrate or suggest a connection of the left coronary artery with either the aorta or pulmonary artery would presumably be the distinguishing feature in these cases, although we have not had angiographic experience with such an entity as yet.

SURGICAL THERAPY

As previously discussed under pathophysiology, the aberrant coronary artery not only fails to supply portions of the myocardium with oxygenated blood at adequate pressure, but may actually function as a left-to-right shunt, draining part of the collateral supply away from the myocardium into the pulmonary artery. The resultant low pressure in the aberrant coronary artery and its branches is apparently the

Table III

SUMMARY OF DIFFERENTIATING FEATURES

	Aberrant Coronary Artery	Endocardial Fibroelastosis
Clinical Features	Symptoms usually appear by age of 3 mo.	Symptoms may appear from infancy through age of 3 yr.
	Murmurs inconspicuous	
Plain Roentgenograms	Marked cardiomegaly, usually recognizable as predominantly left ventricular	
Electrocardiograms	Usually suggest infarction	Usually suggest left ventricular hypertrophy and myocardial changes
Angiocardiograms	Right-side injection may opacify an aberrant coronary artery (2/4 in this series)	
	Left-sided injection shows delayed opacification of left coronary via collateral vessels from the right coronary (2/2 in this series)	Left-sided injection should show normal coronary arteries
	Thin lateral wall of left ventricle which shows no thickening with systole (4/5 in this series)	Slightly thin, normal, or thick left ventricular wall which thickens somewhat with systole
	Dilated, poorly contractile left ventricle, some left atrial enlargement, prolonged circulation time	

most detrimental physiologic consequence of this arrangement. Thus it seems reasonable that simple ligation of the aberrant coronary artery will effect improvement in those cases where retrograde flow in the left coronary artery is demonstrated. Sabiston *et al.*[14] report 3 cases living and markedly improved by this procedure (in combination with pericardiopexy). Theoretically, coronary artery transplant would be the most satisfactory method of therapy. This was actually accomplished in our Case 1, but apparently the stress of operation could not be tolerated and the patient expired. Perhaps earlier recognition and treatment would be more successful. A variety of other methods of treatment have been proposed, including: (a) creation of an artificial ductus from aorta to pulmonary artery; (b) pericardiopexy; (c) constriction of the pulmonary artery beyond the sinuses; (d) insertion of the internal mammary artery into the left ventricle; and (e) anastomosis of a systemic artery into the left coronary.[9]

SUMMARY

Five cases of aberrant coronary artery are presented, with emphasis on the angiographic features and differentiation from endocardial fibroelastosis. Clinical and electrocardiographic features may suggest the proper diagnosis, but only angiography can conclusively demonstrate the continuity between the pulmonary artery and the left coronary artery. In our cases, blood flow was from the pulmonary artery to the coronary artery (forward) in 2 cases, and from the coronary artery to the pulmonary artery (retrograde) in the other 3. When the diagnosis of aberrant coronary artery is suspected, selective left-sided angiocardiography should be the angiographic procedure of choice. The differentiation from endocardial fibroelastosis and other myocardiopathies is usually not a problem with such a study, but may be more difficult with intravenous angiocardiography. With this latter type of study, the coronary arteries are not generally visible, but a persistently thin lateral aspect of the left ventricular wall should suggest the proper diagnosis. Subsequent confirmation by a left-sided injection is advisable.

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COMPLETE TRANSPOSITION OF THE GREAT VESSELS*

ROENTGENOGRAPHIC FINDINGS

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THE roentgenologist dealing with congenital cardiac disease is not unlikely to be confronted with cases in which there is an abnormal relationship between the two great vessels (transposition). Although a number of conditions are characterized by transposed great vessels, the condition of complete transposition seems to be the most common. It seemed appropriate to study the roentgenologic features encountered in a series of 47 patients with this condition who were at our disposal. It was believed that this study not only would portray details of the usual roentgenologic features, but also would emphasize some of the variations that might be encountered.

As there are several conditions characterized by transposition of the great vessels, it is necessary that we define the condition "complete transposition" as used in this report.

In complete transposition there are two ventricles, with or without a defect in the ventricular septum. The aorta, with the coronary arteries arising from it, takes origin from the right ventricle, while the pulmonary trunk takes origin exclusively from the left ventricle. Both atrioventricular valves are patent (thus excluding conditions with tricuspid or mitral valve atresia). The connections of the systemic, pulmonary and coronary veins are normal. Communications between the pulmonary and arterial circulations may occur either by means of a patent ductus arteriosus, a defect in the atrial septum, a defect in the ventricular septum or by a combination of these defects.

MATERIAL AND METHODS

The material presented in this paper represents a series of 47 patients with complete transposition of the great vessels in whom both roentgenologic studies and necropsy specimens were available. Each specimen of the heart was examined for anatomic detail, the results of which are given in a separate report.[4]

The ages at the time of death ranged from 3 days to 3 years; only 6 patients survived beyond the age of 1 year. Twenty-six of the patients were male and 21 female.

The conventional roentgenograms of the thorax of these patients were available for review, and in addition, 29 angiocardiograms were examined. Twenty-three were of the biplane variety.

In considering the entire series of 47 patients, the cases were divided into 3 groups. Group I consisted of 17 cases associated with a ventricular septal defect. In Group II there were 29 cases with an intact ventricular septum. Group III consisted of 1 case with valvular pulmonary stenosis and a ventricular septal defect.

For each case, the conventional roentgenograms were studied in 2 ways. The first consisted of analyzing the size and configuration of the heart. The second way consisted of analyzing the pulmonary vascularity in relationship to: (1) the type of communication between the pulmonary

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and arterial circulations, and (2) the relative size of these communications.

RESULTS

CONVENTIONAL ROENTGENOGRAPHY

Size and Configuration of the Heart. Regardless of the type of communication between the systemic and pulmonary circulations, infants with complete transposition of the great vessels showed mild to moderate degrees of cardiomegaly during the first few weeks of life. Enlargement of the left atrium often occurred and was demonstrated by an indentation deformity on the anterior wall of the barium-filled esophagus below the level of the carina. This was associated, at times, with a slight posterior displacement of this portion of the esophagus. In the frontal projection, the configuration of the heart was usually quite characteristic: it was similar to the shape of an egg tilted so that its long axis lay in an oblique direction. The pole with the least convexity lay upwards and to the right; the pole with the greatest convexity lay downwards and to the left (Fig. 1, *a–i;* and 2, *a–i*). On occasion, a roentgenogram of the thorax was made during partial expiration.

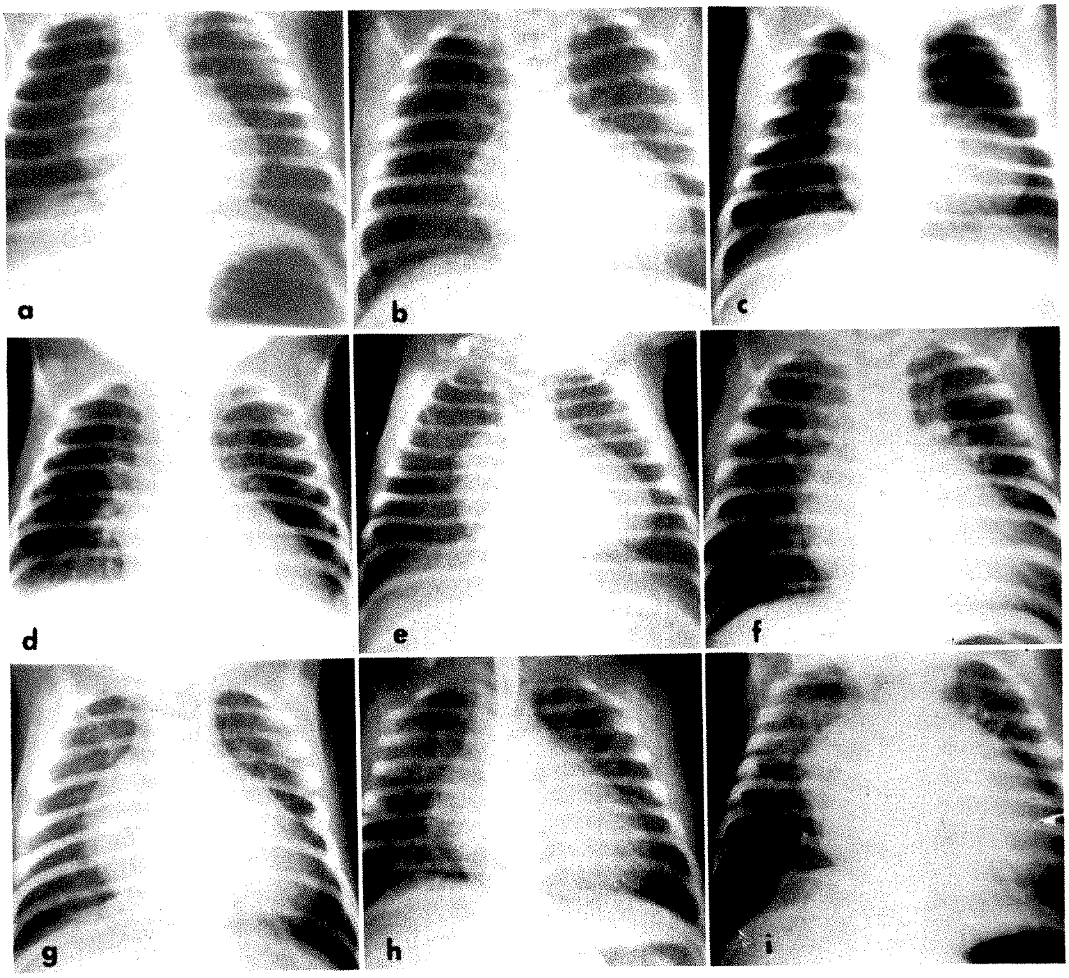

Fig. 1. Cases of complete transposition of the great vessels with intact ventricular septum. Series of frontal chest roentgenograms. (*a*) Female, aged 7 days; no ductus; (*b*) male, aged 7 days; no ductus; (*c*) female, aged 10 days; no ductus; (*d*) female, aged 4 days; 4 mm. patent ductus; (*e*) male, aged 2 days; 1.5 mm. patent ductus; (*f*) male, aged 5 weeks; 2 mm. patent ductus; (*g*) male, aged 6 days; 4 mm. patent ductus; (*h*) female, aged 13 days; 4 mm. patent ductus; (*i*) male, aged 2 months; 1.5 mm. patent ductus.

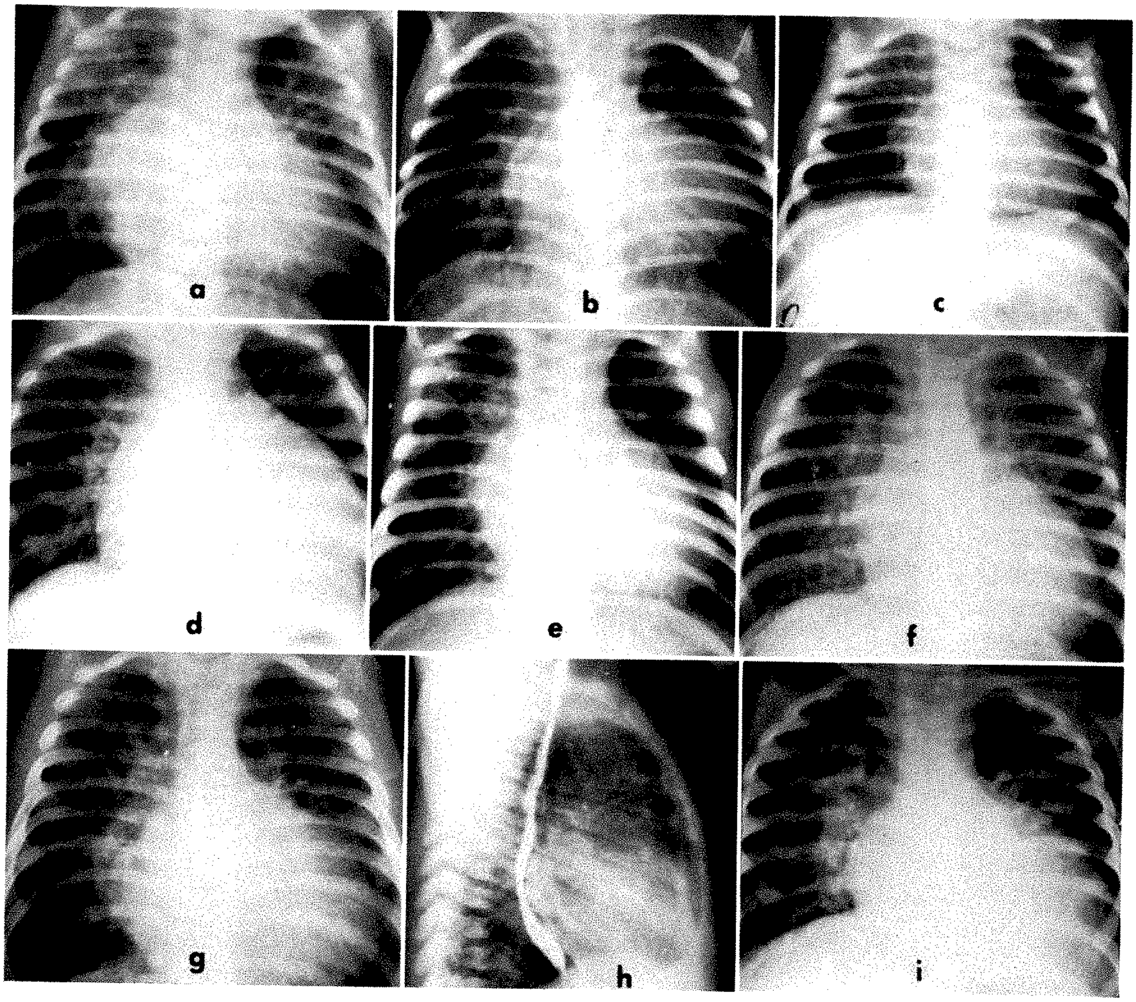

Fig. 2. Complete transposition of the great vessels with ventricular septal defect (VSD). Series of frontal chest roentgenograms. (*a*) Male, newborn; 12 mm. VSD; (*b*) female, aged 2 weeks; 8 mm. VSD; (*c*) male, aged 3 weeks; small muscular VSD; (*d*) same patient as shown in *c*; roentgenogram made at age 2 years and 3 months. The heart is now markedly enlarged; (*e*) male, aged 1 month; 2 mm. VSD; (*f*) female, aged 7 weeks; 8 mm. VSD; (*g*) male, aged 5 months; large VSD; (*h*) same patient as *g*. Lateral view with barium to show the presence of left atrial enlargement commonly associated with this condition; (*i*) female, aged one year and 3 months; 1.5 cm. VSD.

Under such circumstances the long axis of the cardiac density appeared horizontal (Fig. 1*c*).

Thymic tissue was usually not visualized. This feature, and the abnormal relationship of the two great vessels, probably accounted for the narrow appearance of the superior mediastinum. The right side of the superior mediastinum often showed a narrow vertical band of increased density; the lateral margin of this density was formed by the superior vena cava. In a few instances, this lateral margin was slightly convex owing to the displacement of the superior vena cava by an enlarged transposed aorta (Fig. 2*f*). Rarely, this density was quite prominent and exhibited a bulging right lateral margin; in this instance, moderate displacement of the superior vena cava by a right aortic arch was demonstrated (Fig. 3, *a*–*f*; note Fig. 3*a*). Infants who survived the first few weeks or months of life invariably showed a gradual increase in cardiac size. Ultimately, the heart became

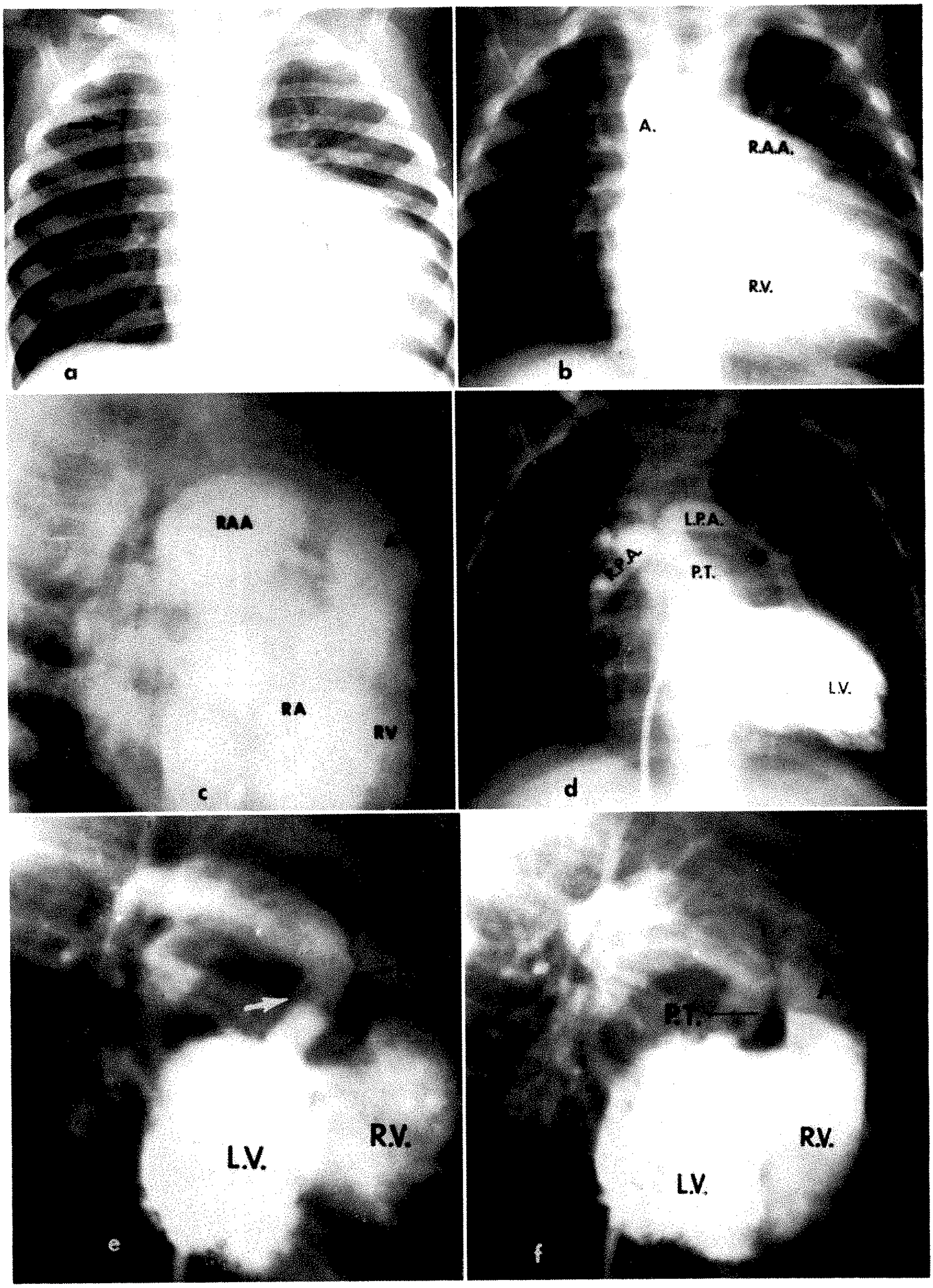

FIG. 3. Roentgenographic studies of a case of complete transposition of the great vessels with ventricular septal defect, pulmonary valvular stenosis and right aortic arch. (*a*) Frontal roentgenogram of the chest showing cardiomegaly. The pulmonary vasculature is within normal limits. Density in the right superior mediastinum (arrow) is produced by the lateral displacement of the right superior vena cava by the right

quite enlarged and showed a tendency to assume a globular shape (Fig. 2, *c* and *d*).

Pulmonary Vascularity. In the 29 infants comprising Group I (intact ventricular septum), 19 were 1 month of age or less. Among these 19 infants, 11 showed pulmonary vasculature which was interpreted as being within normal limits. Of these 11, measurements of the internal diameter of the ductus arteriosus at necropsy revealed that 6 had a closed ductus arteriosus, while 4 showed a narrow ductus arteriosus of 2 mm. or less. In the remaining case, the size of the ductus arteriosus was not recorded. The remaining 8 infants demonstrated an obvious *increase* in pulmonary vascularity. Of these, 6 had a patent ductus arteriosus, 3 mm. or more in internal diameter, while only 1 had a patent ductus arteriosus of less than 3 mm. in diameter. In the remaining case the size of the ductus was not recorded.

The remaining 10 infants in Group I were 1 month of age or older and each showed an obvious increase in pulmonary vascularity. Three of these cases showed a patent ductus arteriosus 2 mm. in width, 2 had a patent ductus arteriosus 1 mm. in diameter, and 1 had a 4 mm. patent ductus arteriosus. In the remaining 4 cases the size of the ductus was not recorded.

In the 17 patients comprising Group II (ventricular septal defect), 15 showed increased pulmonary vascularity regardless of age or the size of the defect. Two cases did not exhibit increased pulmonary vasculature and both revealed a small ventricular septal defect.*

The 1 case in Group III associated with pulmonary stenosis and ventricular septal defect showed pronounced decrease in pulmonary vascularity. In addition, an enlarged right aortic arch was present.

Comment. Complete transposition of the great vessels may or may not elicit an obvious increase in pulmonary vasculature. According to our results, those patients less than 1 month of age having an intact ventricular septum and a narrow or closed ductus arteriosus characteristically showed no obvious increase in pulmonary vasculature (Fig. 1, *a*, *c* and *e*), whereas those with an intact ventricular septum and a wide open ductus arteriosus (3 mm. or more) usually showed an increase in pulmonary vascularity. However, in the patients with an intact ventricular septum 1 month of age or more, the size of the ductus arteriosus appeared to be of little consequence, inasmuch as the vascularity was increased in each case regardless of the anatomic state of the ductus arteriosus. Among the patients in Group II (ventricular septal defect), all but 2 showed an increase in pulmonary vascularity despite the age of the patient.

Thus, among patients with increased vascularity observed during the first few weeks of life, the roentgenogram cannot distinguish between an intact ventricular septum with a wide patent ductus arteriosus and a ventricular septal defect.

It should be emphasized that although an interatrial communication was present in each case studied, this took the form either of a valvular competent foramen ovale or a *small* atrial septal defect.

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* Small ventricular septal defect: a defect of less than 1 cm. per m.^{2} of body surface area.

sided, transposed aorta. (*b* and *c*) Selective angiocardiograms. Frontal and lateral views. The tip of the injection catheter is in the right atrium. Note the unusual position of the right atrial appendage (juxtaposition of the right atrial appendage). (*d*, *e* and *f*) Selective studies from the left ventricle. Frontal and lateral views. Arrow points to the valvular pulmonary stenosis, best seen on the lateral views. Contrast medium enters the right ventricle via the ventricular septal defect and then enters the transposed aorta. A = aorta; RAA = right atrial appendage; RA = right atrium; RV = right ventricle; RPA = right pulmonary artery; LPA = left pulmonary artery; PT = pulmonary trunk; LV = left ventricle.

ANGIOCARDIOGRAPHY

As previously indicated, angiocardiograms were available in 29 patients. Of these 29, 12 exhibited an intact ventricular septum (Group I), 16 a ventricular septal defect (Group II), and 1 pulmonary stenosis with a ventricular septal defect (Group III).

General Considerations. Forward angiography is effective in demonstrating many of the features of complete transposition. Following opacification of the inferior vena cava, there was usually dense opacification of an enlarged right atrium. The right atrial appendage was moderately enlarged and more trabeculated than normal. The apex of this structure may extend across the midline in the frontal projection (Fig. 4, *a* and *b;* note particularly 4*b*). In 2 cases, juxtaposition of the atrial appendages was evident (Fig. 3, *b* and *c*).

Early opacification of an enlarged left atrial chamber was a common finding. In our series of cases, a right-to-left shunt at the atrial level was detected in 11 of the 17 angiocardiograms reviewed in the group with intact ventricular septum. This finding was present in 3 of the 12 angiocardiograms available in the group with ventricular septal defect.

Following opacification of the right atrium, there was usually very definite opacification of an enlarged right ventricular chamber which lay anteriorly in the lateral view. Subsequent to this, dense opacification of the aorta was invariably noted. The ductus arteriosus when patent was often identified.

The position and configuration of the aorta in both the frontal and lateral views varied from case to case. In the frontal view, the site of origin of the aorta showed 3 variations in relationship to the thoracic spine.

In the majority of cases, the origin of the aorta *overlay* the thoracic spine, the ascending aorta coursed vertically upward, and then arched downward to become continuous with the descending thoracic aorta, thus producing a high narrow arch (Fig. 5, *b* and *e;* and 7*c*). At other times, the ascending aorta exhibited a convexity that flared outward and to the right of the upper thoracic spine before crossing the midline to become continuous with the descending thoracic aorta. The resultant configuration was a wide arch (Fig. 8, *c* and *e*).

Rarely, the origin of the aorta lay to the *right* of the thoracic spine, and under these

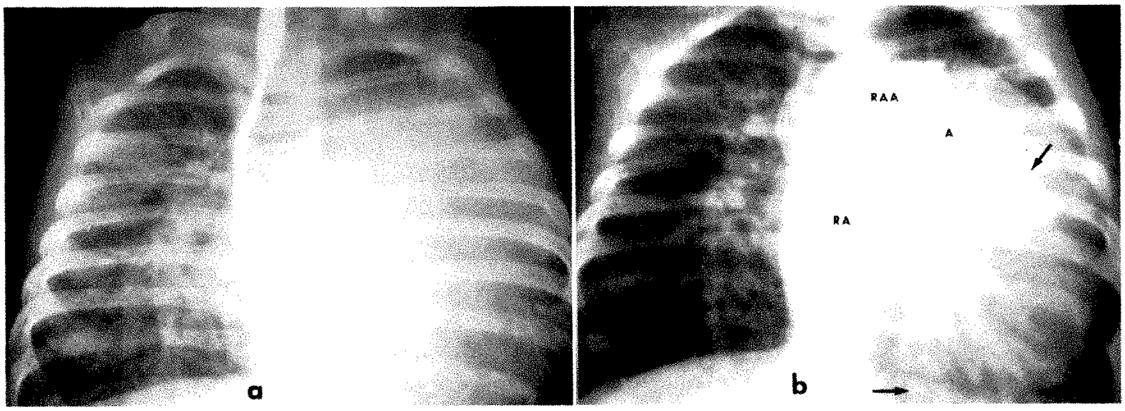

Fig. 4. Complete transposition of the great vessels with ventricular septal defect. Unusual angiocardiographic features. Female, aged 5 months. (*a*) Frontal roentgenogram of the chest showing marked cardiomegaly and increased pulmonary vasculature. (*b*) Forward angiocardiogram. Frontal view. Marked enlargement of the right atrial appendage (RAA) which projects to the left of the spinal column. At autopsy the patient exhibited a large VSD (7 mm.) above the crista. In addition, a peculiar recess was observed in the upper portion of the right ventricular chamber (arrow). RA = right atrium; A = aorta.

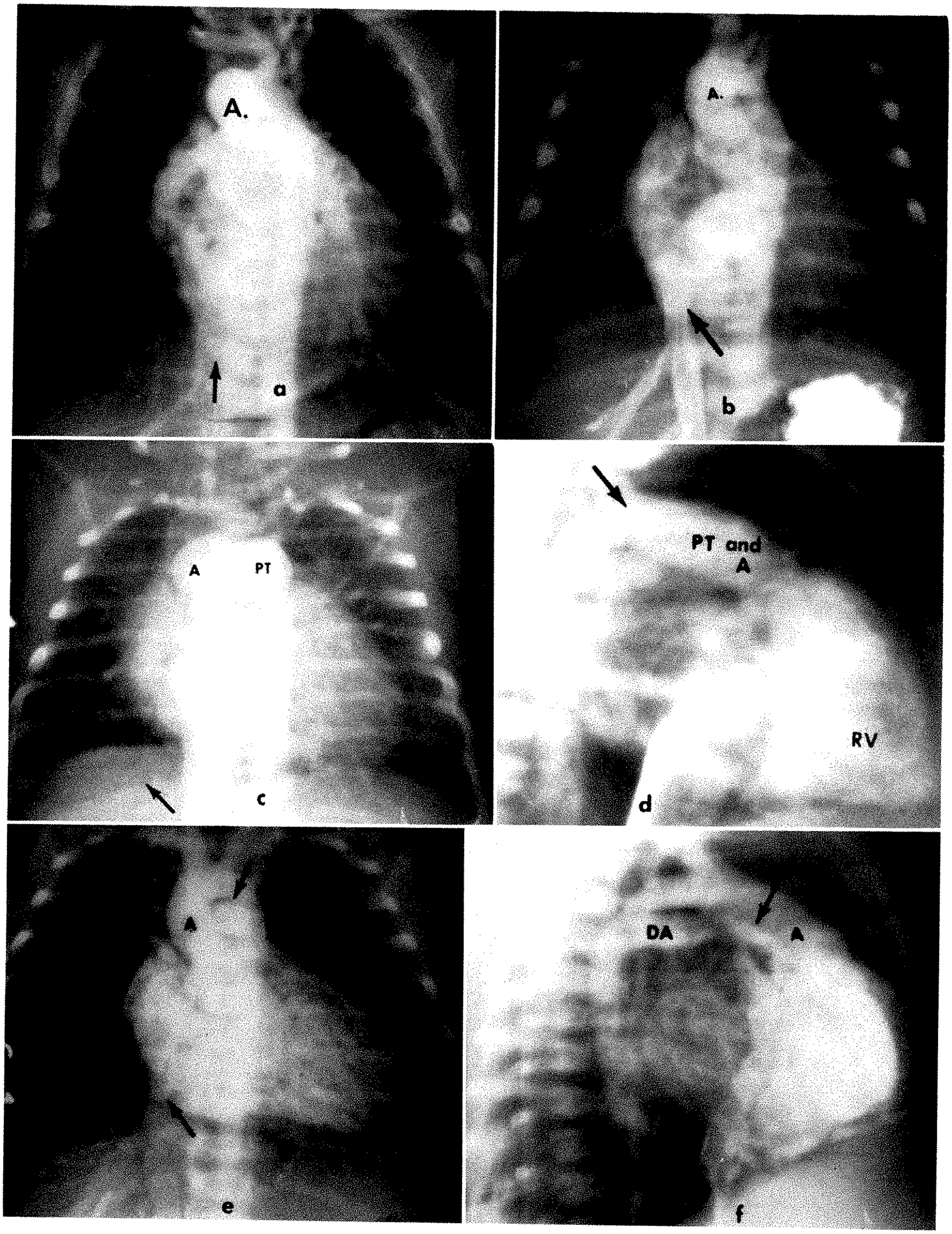

FIG. 5. Complete transposition of the great vessels with intact ventricular septum. Angiocardiographic findings. Variations in the position of the aorta and pulmonary trunk. (*a* and *b*) Ascending aorta superimposed over the thoracic spine. Pulmonary trunk lies directly posterior to the aorta (A). (*c*) Pulmonary trunk (PT) lies to the left of the aorta. (*d*) Lateral view of *c*, pulmonary trunk and aorta superimposed. The arrow points to the superior margin of the pulmonary trunk. (*e* and *f*) Frontal and lateral views. The pulmonary trunk lies posterior and to the left of the aorta. A large patent ductus arteriosus (DA) is seen on the lateral view. In the above figure (and in subsequent figures) the arrow, when present at the bottom of each roentgenogram, indicates the degree of rotation of the patient during the roentgenographic study. Arrow (↑) indicates no rotation. Arrow (↖) indicates minimal rotation to the right. Arrow (↗) indicates minimal rotation to the left. Arrow (←) indicates moderate rotation to the right. Arrow (→) indicates moderate rotation to the left.

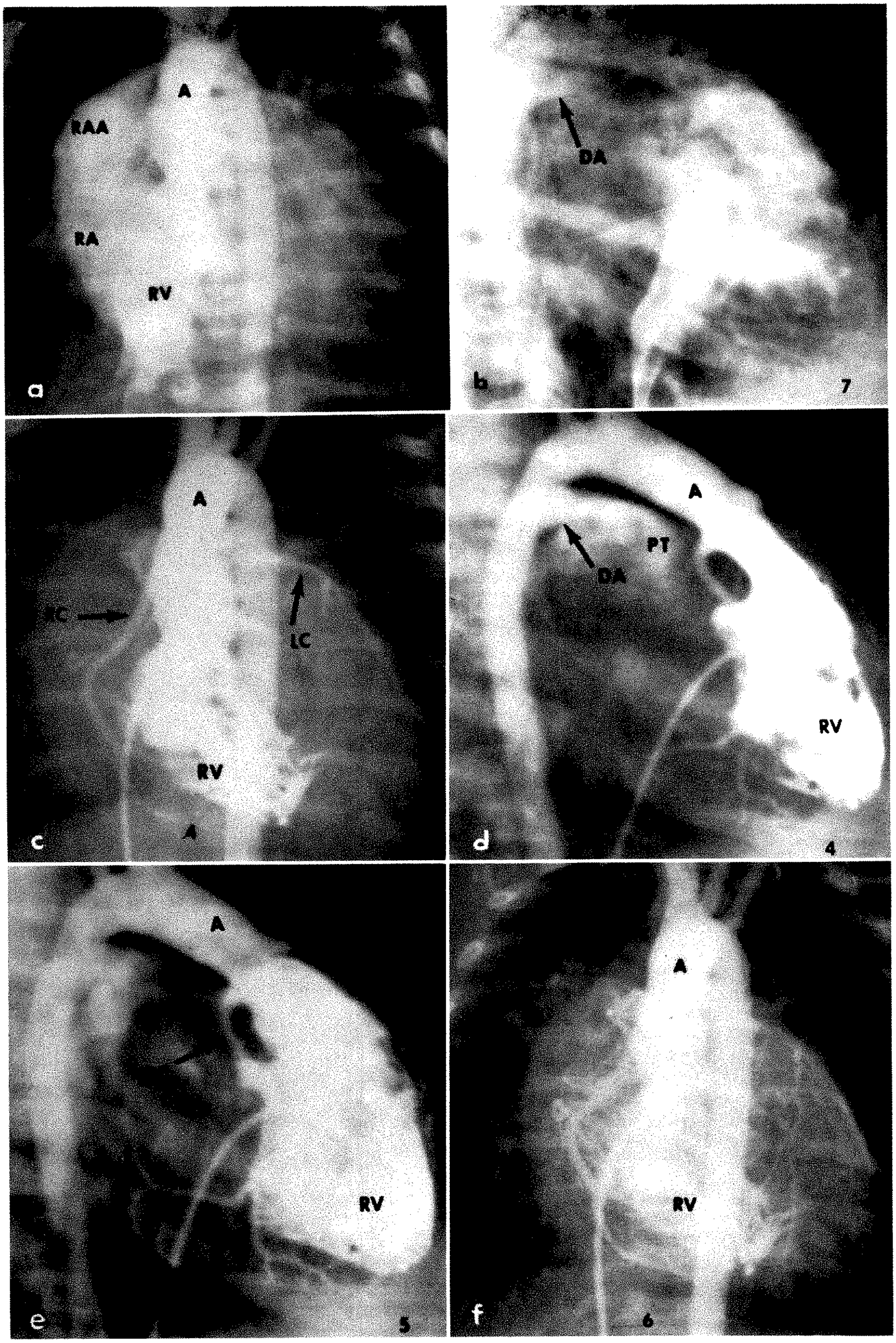

FIG. 6. Transposition of the great vessels with intact septum. (*a* and *b*) Forward angiocardiograms. Frontal and lateral views. Sequential opacification of the right atrium (RA), right ventricle (RV) and transposed

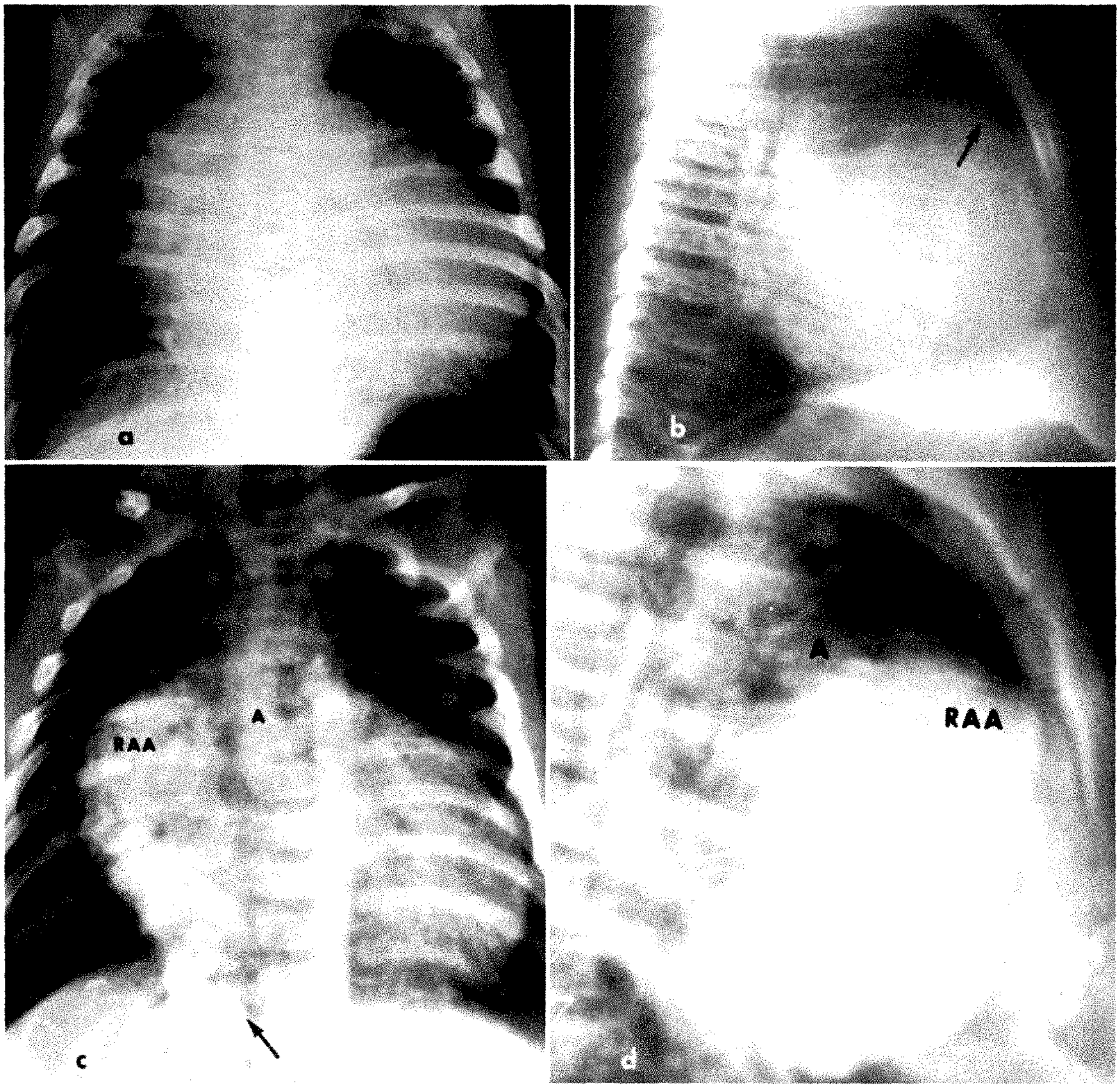

Fig. 7. Complete transposition of the great vessels with intact ventricular septum. Unusual angiocardiographic features. Female, aged 9 weeks. (*a* and *b*) Frontal and lateral roentgenograms of the thorax show marked cardiomegaly with increased pulmonary vasculature. An unusual prominence of the anterior superior portion of the cardiac density is seen on the lateral view (arrow). (*c* and *d*) Forward angiocardiograms indicated that this density was due to the markedly enlarged right atrial appendage (RAA). In addition, the right ventricular chamber was markedly hypertrophied in its outflow portion, and this feature probably accounted for the more posterior position of the ascending aorta (A) on the lateral view.

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aorta (A). A large patent ductus arteriosus (DA) is seen on the lateral view. (*c*, *d*, *e* and *f*) Same patient Series of roentgenograms made during right ventriculography. The coronary arteries are well outlined. Right coronary preponderance. Large patent ductus arteriosus (DA). On the initial lateral roentgenogram of this study, the contrast medium fills a portion of the pulmonary trunk via the ductus; and on the subsequent lateral roentgenogram made $\frac{1}{5}$ of a second later, the pulmonary trunk is no longer opacified, presumably owing to a flushing out of the contrast medium by unopacified blood entering the pulmonary trunk from the left ventricle. RAA = right atrial appendage; PT = pulmonary trunk; LC = left coronary artery; RC = right coronary artery.

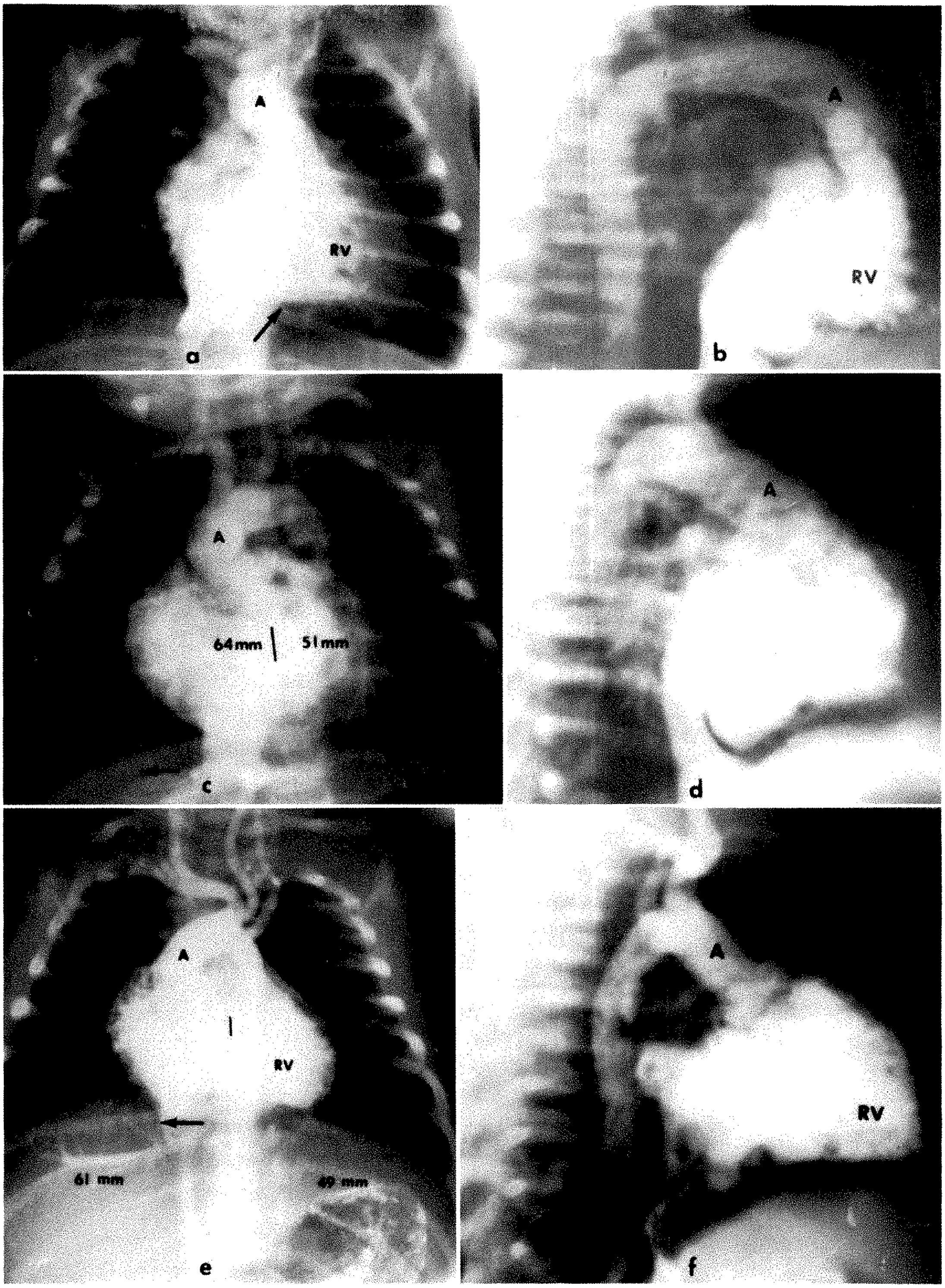

FIG. 8. Complete transposition of the great vessels with intact ventricular septum. Angiocardiographic findings. Variations in the configuration and position of the aorta. (*a* and *b*) Frontal and lateral views. Aorta (A) arises to the left of the thoracic spine. (*c* and *d*) Frontal and lateral views. Aorta arises to the right of the thoracic spine. The degree of rotation is indicated by the difference in the measurement between the

circumstances the aortic arch appeared even wider (Fig. 9, *a* and *e*).

In other cases the origin of the aorta lay to the *left* of the thoracic spine. As a result, there was no visible "arch" in the frontal view since the density of the ascending aorta was superimposed upon the density of the descending thoracic aorta (Fig. 8*a* and 9*c*).

In the lateral view, the anteriorly placed aorta usually arched upward and backward in a gentle curve from its site of origin to become continuous with the descending thoracic aorta (Fig. 5, *d* and *f*; and 8*b*), or it coursed obliquely upward and backward in a straight line, angling sharply downward to become the descending thoracic aorta (Fig. 8*f* and 9*b*).

The relationship of the aorta to the pulmonary trunk was variable. Poor opacification of the pulmonary trunk was a common finding since the major portion of the contrast medium passed directly from the right ventricle into the aorta. Opacification of the left side of the heart was often inadequate for proper evaluation of anatomic detail.

Of the 23 biplane angiocardiograms reviewed, enough opacification of the pulmonary trunk was present in 15 to evaluate the relationship of this structure to the aorta.

In a *pathologic* study by one of us (L. P. E.[4]), the external relationship of the aorta and pulmonary trunk showed 3 types. In Type I (most common), the aorta was situated anterior and to the right of the pulmonary trunk in an *oblique* relationship. In Type II (less common), the aorta was situated to the right of the pulmonary trunk in a *side-to-side* relationship. In Type III (uncommon), the pulmonary trunk lay directly *posterior* to the aorta.

Among the foregoing 15 cases, the great vessels as viewed angiocardiographically showed the following: 10 patients exhibited the Type III (anteroposterior) great vessel arrangement (Fig. 5*a*; and 6, *a*–*f*); 4 cases revealed the Type I (oblique) arrangement (Fig. 5, *e* and *f*); and in 1 case, the pulmonary trunk and aorta showed the Type II (side-to-side) relationship with the pulmonary artery to the left of the aorta (Fig. 5, *c* and *d*).

DISCUSSION

Cases of complete transposition of the great vessels with two ventricular chambers lend themselves for discussion in 2 groups: (1) those cases without pulmonary stenosis and (2) those cases associated with pulmonary stenosis.

In many cases of complete transposition of the great vessels either with an intact ventricular septum or a ventricular septal defect (without pulmonary stenosis), there is a fairly characteristic configuration of the heart on the conventional roentgenograms. Although this configuration on frontal roentgenograms is not entirely specific for complete transposition, when it is found associated with a definite increase in the pulmonary vasculature in a cyanotic infant, the condition "complete transposition"

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midpoint of the thoracic spine and the margin of the bony thorax on each side. (*e* and *f*) Frontal and lateral views. Aorta arises to the right of the thoracic spine. Again there is moderate rotation to the right side. The measurement between the midpoint of the thoracic spine and the bony thorax on each side was made at the level of the vertical black mark overlying the thoracic spine. Note the difference in the configuration of the aorta on the lateral views. The angulated appearance in *d* and *f* was most commonly associated with those cases in which the aorta arose to the right of the thoracic spine. The configuration of the aorta in *b* was most commonly associated with those cases in which the aorta arose to the left of the thoracic spine. RV = right ventricle.

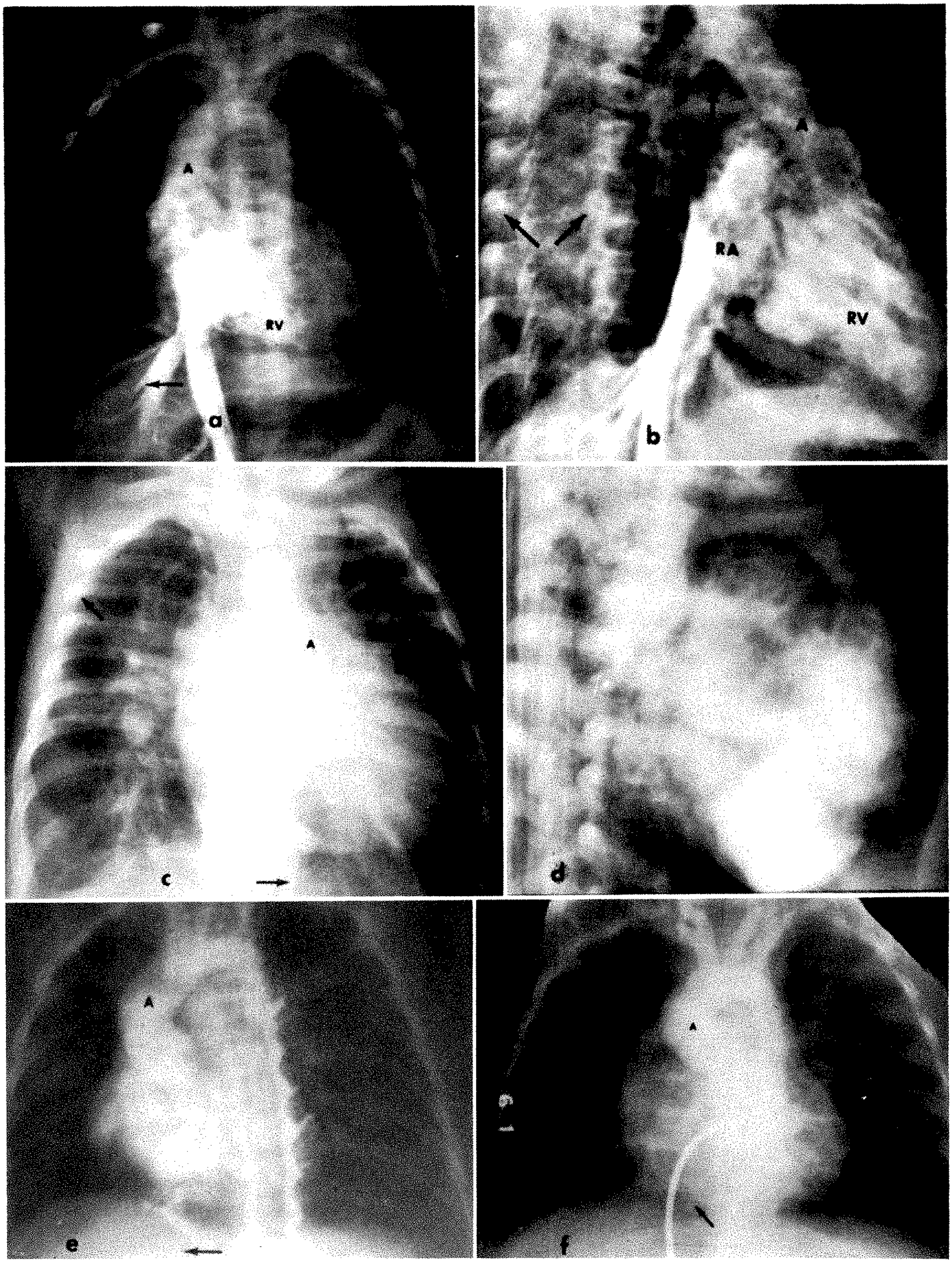

FIG. 9. Complete transposition of the great vessels with ventricular septal defect. Angiocardiographic findings. Variations in the position and configuration of the aorta. (*a* and *b*) Frontal and lateral views. Aorta (A) arises to the right of thoracic spine. Rotation of the patient to the right is present as indicated by the asymmetry of the ribs on the frontal view and the appearance of the thoracic spine and posterior portions of the ribs on the lateral view. (*c* and *d*) Frontal and lateral views. Aorta arises to the left of the thoracic

should be the primary diagnosis. The absence of increased pulmonary vasculature, however, does not rule out complete transposition, since 11 of 19 infants (1 month of age or less) in the group with an intact ventricular septum and 2 cases in the group with ventricular septal defect showed pulmonary vasculature which was interpreted as being within normal limits.

The variation in the position of the origin of the aorta in frontal angiocardiographic views has been demonstrated by several authors.[1–3,5–8] Variations in position and configuration of the aorta in frontal and lateral angiocardiographic views were noted also in our series. In contrast to previous reports, we have been impressed by the *degree* of rotation of the patient during the roentgenographic study as being the prime factor in producing changes in the position of the aorta. Since angiocardiographic studies are usually performed with the patient supine, the proximal part of the *ascending aorta* is in an anterior-substernal position. Under such circumstances, rotation of the patient will readily project the ascending aorta to the left, or to the right, of the thoracic spine, depending upon the direction of rotation. To support these findings, we deliberately rotated several infants prior to the angiocardiographic procedure and found that it was possible to project the proximal ascending aorta to either side of the thoracic spine.

In some cases, in lateral angiocardiograms, the junction of the distal part of the aortic arch and the proximal part of the descending thoracic aorta appeared angular (Fig. 8, *d* and *f*; and 9*d*). This configuration was commonly associated with a "wide arch" which arose to the right, or flared to the right, of the thoracic spine in the companion frontal view. Inspection of the roentgenograms in these cases often revealed evidence of rotation of the patient to the right. In other instances, the lateral view showed the aorta proceeding upward and posteriorly to join the descending thoracic aorta in a gradually arching manner (Fig. 8*b*; and 9*d*). In some of these cases the origin of the aorta appeared to lie to the left of the thoracic spine on the companion frontal roentgenogram and evidence of rotation of the patient to the left was demonstrated.

Castellanos and associates[2] described 7 cases of complete transposition. Of these 7, angiocardiograms were available in 3. Two of these appeared typical; the third case, however, exhibited an aorta in the frontal view which appeared to arise to the left of the thoracic spine. In this case, rotation of the patient to the left may be detected. Cooley and Sloan[3] divided complete transposition of the great vessels into 6 groups. Review of the angiocardiographic data in this article would tend to indicate the role of rotation in accentuating the position of the aorta. Most of the roentgenograms in their cases appeared quite typical, inasmuch as there was no evidence of rotation of the patient. However, Case 1 in Group IV in their study showed an aorta arising far to the right of the thoracic spine and

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spine. Rotation of the patient to the left is indicated by the asymmetry of the ribs on the frontal view and the appearance of the thoracic spine and posterior portions of the ribs on the lateral view. Note again the configuration of the aorta in *b* as opposed to *d*. (*e* and *f*) Frontal angiocardiograms made on the *same patient at different times*. The aorta in *e* arises well to the right of the thoracic spine and rotation of the patient to the right is obvious. In *f* the patient was well positioned and only minimal rotation to the right is present. On this roentgenogram the origin of the aorta overlies the thoracic spine.

coursing to the left in a "wide arch" to reach the descending thoracic aorta. In this example, the patient, as judged by the published roentgenograms, appears to have been rotated to the right. In Case 2 in Group v in their study the aorta arose far to the left of the thoracic spine and, in this instance, rotation of the patient to the left may be detected.

The difficulty of demonstrating the presence of a ventricular septal defect in cases of complete transposition without pulmonary stenosis by the use of forward angiocardiography has been commented upon by Keith and his group.[6] In the absence of a right-to-left shunt at the atrial level, the presence of a ventricular septal defect may be suspected if there is evidence of simultaneous opacification of both great vessels immediately following opacification of the right ventricle. If, however, there is immediate filling of the left side of the heart through an interatrial communication in the early part of the study, simultaneous opacification of both great vessels is not reliable as a sign of a ventricular septal defect. Under these circumstances the contrast medium from the left side of the heart will reach the pulmonary artery at approximately the same time as the medium from the right side of the heart reaches the aorta. In such instances, a ventricular septal defect may be defined with the use of selective right ventriculography, a technique which should be utilized in conjunction with left-sided injection, if possible.

In those patients in which there is a demonstrable right-to-left shunt at the atrial level, it has been impossible to distinguish the nature of the communication between the atria in terms of whether the flow was through an atrial septal defect or a patent foramen ovale.

In contrast to the distribution of the great vessel patterns observed by one of us (L. P. E.[1]), the Type III (anteroposterior) great vessel relationship was observed commonly in this study, and less commonly in the anatomic study. Moreover, the Type II (side-to-side) great vessel pattern was observed commonly in the anatomic study, and in only 1 case angiocardiographically. The reason for this discrepancy is not clear. Several factors may be responsible. First, in the angiocardiographic study of the relationship of the great vessels, only 15 cases were available for a study, whereas, in the anatomic study, 54 cases were available for analysis. Secondly, ideal opacification of the pulmonary artery is often not obtained during forward angiocardiography, resulting in loss of definition of the actual wall of the pulmonary trunk. In this situation the great vessels, which appear to be anteroposterior in the frontal view, may in reality be obliquely arranged. Finally, rotation of the patient during the roentgenographic study may play a role but certainly not to the degree that it does in determining the relationship of the ascending aorta to the thoracic spine, since the pulmonary artery and the aorta are more closely related.

Turning now to cases of complete transposition with pulmonary stenosis, it would seem, judging from cases reported in the literature and those observed at this institution, that the roentgen appearance is often bizarre. Decreased pulmonary vasculature, an unusual configuration of the heart (dextroversion) or a right aortic arch may be present (2 cases in the anatomic study, 1 of which is the case herein reported, revealed a right aortic arch). With milder degrees of pulmonary stenosis, the pulmonary vasculature may appear normal. Selective angiocardiograms from the left ventricle will demonstrate the presence and degree of pulmonary stenosis (Fig. 3, *d-f*).

SUMMARY

The roentgenologic features of 47 patients with complete transposition of the great vessels studied at necropsy have been reviewed.

On conventional roentgenograms of the thorax, the configuration of the heart was quite uniform. Cases associated with a ventricular septal defect usually showed increased pulmonary vasculature from birth.

Many cases associated with an intact ventricular septum, particularly those with a small or closed ductus arteriosus, will show normal pulmonary vasculature during the first few weeks of life. On the other hand, those with an intact ventricular septum and a wide patent ductus arteriosus usually show increased pulmonary vascularity.

Variations in the angiocardiographic features of this condition with special reference to the configuration of the aorta have been shown. It is suggested that rotation of the patient during the roentgenographic study plays a significant role in the production of these variations.

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ROTATIONAL CINEANGIOCARDIOGRAPHY*

By LUCIEN CAMPEAU, M.D., F.R.C.P.(C),† *and* JACQUES SALTIEL, M.D.‡
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ANGIOCARDIOGRAPHY of most congenital heart diseases frequently requires at least two projections. Conventional biplane angiocardiography fulfills this requirement; however, single plane cineangiocardiography, which is used most often at present, necessitates separate studies in different positions. Since contrast media are frequently not well tolerated, particularly by cyanotic patients, a satisfactory technique employing a single injection is desirable. In the technique described herein cineangiocardiographic examinations in multiple successive planes are made following a single injection of contrast medium.

TECHNIQUE AND MATERIAL

The cineangiocardiography in multiple successive planes is performed during rapid body rotation. This is achieved by turning a platform on which the patient is firmly secured. A bearing support permits a 180 degree rotation of the platform, although a rotation of 90 degrees from the lateral to the frontal position is most commonly employed. This platform is adjusted below the axis of the rotating crank shaft at a distance such that the heart remains within view during rotation (Fig. 1, *A–C*). The supports bearing the rotatable platform are then firmly fixed to the top of a Universal Picker X-Ray table, which is used for cardiac catheterization. Sodium diprotrizoate and sodium diatrizoate in amounts of 1 cc. per kg. of body weight are injected under pressures of 4 to 8 kg. per cm.^{2} with an automatic Gidlund syringe. An 8 inch Picker image amplifier and a 16 mm. cinecamera are used. Rapid manual rotation of the platform is begun as soon as the radiopaque substance appears at the site of injection. Twenty-two such examinations were performed on 20 children, all below 6 years of age. In 16—cases of tetralogy of Fallot, pure pulmonic stenosis and complete transposition—the 90 degree angle of rotation, from the left lateral to the frontal plane was used. In 2 cases of coarctation of the aorta, the rotation was carried out from a 45 degree left anterior oblique position to the frontal position; in a case of hypertrophic subvalvular aortic stenosis and another of stenosis of the pulmonary arteries, the rotation was from a 45 degree left anterior oblique position to a 45 degree right anterior oblique position.

RESULTS

Our limited experience demonstrated the feasibility of obtaining cineangiocardiograms in multiple successive planes covering as much as a 90 degree angle of rotation. In this manner, both frontal and lateral cineangiocardiograms could be obtained in addition to all oblique planes included in a 90 degree angle following a single injection of radiopaque substance (Figs. 2 through 4, inclusive). The various structures are opacified in succession as the contrast medium progresses in the direction of blood flow and these are visualized in different projections during the body rotation. Earlier opacified structures are seen in the projections nearest the initial projection chosen at the beginning of the examination, whereas later opacified structures are demonstrated in other projections at the end of rotation. It is therefore advisable to start this examination in the position most suitable for the study of the structures to be opacified at the onset, and then, to rotate

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the patient in time to visualize the other structures which become opacified later and are best shown in these later projections. The value of this approach is illustrated in a case of tetralogy of Fallot (Fig. 3, *A*, *B* and *C*). The outflow tract of the right venticle, best studied in the lateral and left anterior oblique planes, is opacified at the beginning of rotation; the infundibular and pulmonary valve stenoses are well demonstrated even though the pulmonary artery is not yet entirely opacified (Fig. 3*A*). As the patient is turned to the left anterior oblique position, the contrast medium opacifies the aorta and the left ventricle (Fig. 3*B*; and Fig. 4, *A*, *B* and *C*). During this rotation from the left lateral to the left anterior oblique position, the interventricular septum becomes perpendicular to the screen and is well demonstrated whenever both ventricles are opacified. By the time the patient is in the frontal plane, the large vessels are filled with opaque substance (Fig. 3*C*), and the size and position of the pulmonary arteries, aortic arch and subclavian arteries may then be evaluated.

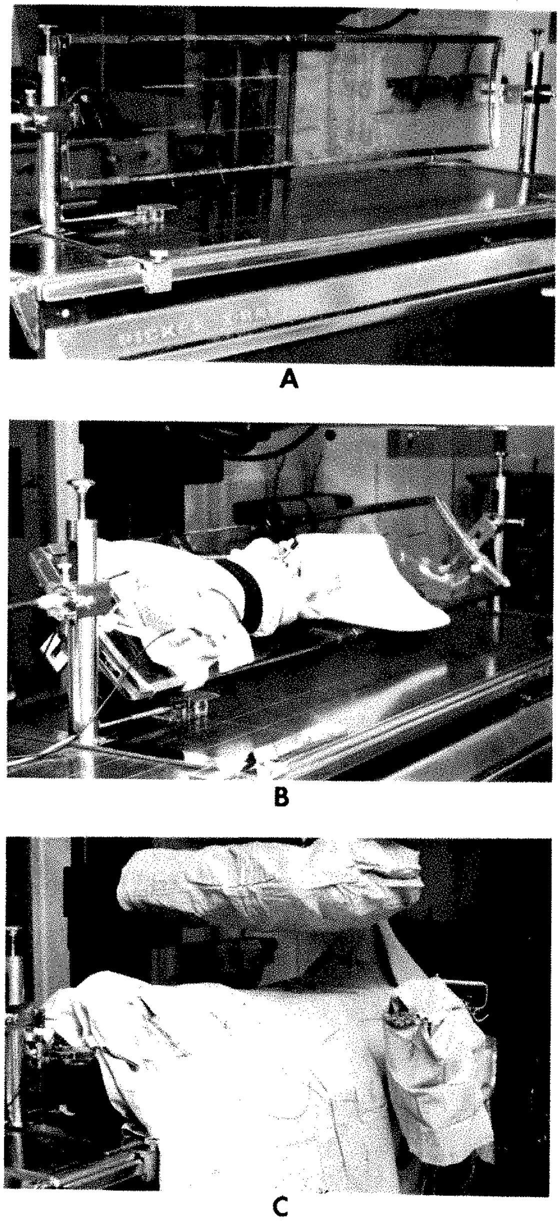

Fig. 1. Rotatable platform in three different positions: (*A*) lateral; (*B*) left anterior oblique; and (*C*) frontal position. The patient is firmly secured by belts at the level of the thorax, abdomen, legs and arms. The head is also immobilized to prevent whipping during the rapid manual rotation (*B*).

It was found after the first trials that, if rapid rotation was started as soon as the contrast medium appeared at the site of injection, both frontal and lateral views proved to be satisfactory. In 2 earlier cases of tetralogy of Fallot, the examination was repeated because rotation had been too slow in one case and too fast in the other. In 4 other cases of tetralogy of Fallot, a second study was obtained in the anteroposterior position. The frontal projection had been inadequate in 1 case because of slow rotation but it had been satisfactory in the other 3. The repeat studies in the frontal projection in these latter 3 cases did not give better images than those obtained with the rotation technique. In one case, however, a case suspected to have a tetralogy of Fallot, the aorta did not opacify after injection into the right ventricle below the pulmonic valve, but after a repeat injection into the right ventricular inflow tract, the frontal cineangiocardiograms showed early opacification of the aorta.

The cineangiocardiograms obtained in this fashion in 3 cases of pure pulmonic valve stenosis were satisfactory (Fig. 2, *A*–*D*).

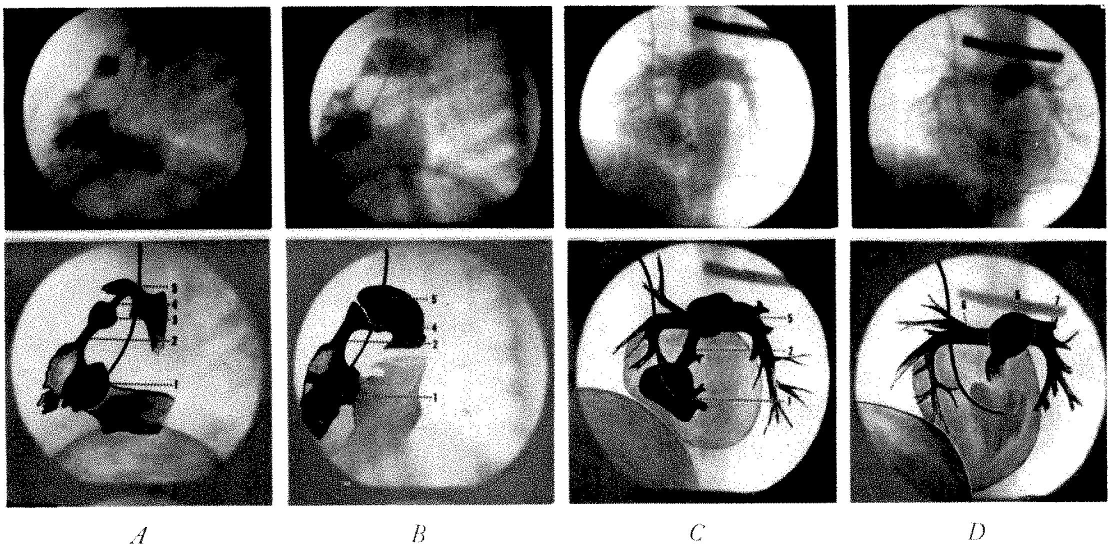

FIG. 2. *Top.* (*A*, *B*, *C* and *D*) Single frames of cineangiocardiograms, made during body rotation from left lateral to the anteroposterior position following a single injection of radiopaque substance, show pulmonary valve stenosis. (*A*) Frontal position; (*B*) left anterior oblique position at approximately 75 degrees; (*C*) left anterior oblique position at approximately 45 degrees; (*D*) approaching the frontal plane.

Bottom. (*A*, *B*, *C* and *D*) Schematic drawings traced from the enlarged cineangiocardiographic image: 1—right ventricle; 2—infundibular stenosis; 3—so-called third chamber with dome shaped pulmonary valve; 4 in *A*—jet of radiopaque substance passing through the stenotic valve; 4 in *B*—pulmonary valve; 5—main pulmonary artery; 6—right pulmonary artery; 7—left pulmonary artery.

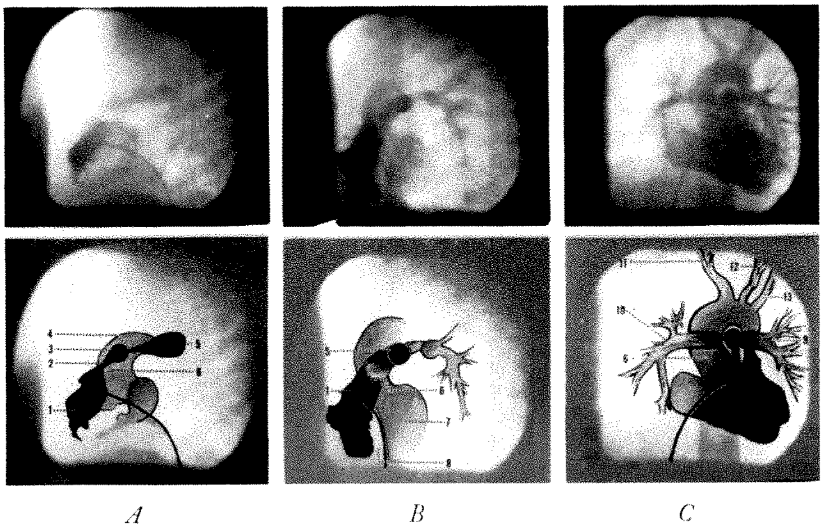

FIG. 3. *Top.* (*A*, *B* and *C*) Single frames of cineangiocardiograms taken during body rotation from left lateral to the anteroposterior position following a single injection of radiopaque substance in the right ventricle in a case of tetralogy of Fallot. (*A*) Pulmonary valve and infundibular stenosis in the left lateral projection; (*B*) ventricular septal effect and slight to no overriding of the aorta in a 75 degree left anterior oblique position; (*C*) good opacification of the pulmonary arteries, aorta, brachiocephalic and left subclavian arteries in the frontal plane.

Bottom. (*A*, *B* and *C*) Schematic drawings traced from the enlarged cineangiocardiographic image: 1—right ventricle; 2—infundibular stenosis; 3—dome shaped pulmonary valve; 4—jet of contrast medium passing through the stenotic valve; 5—pulmonary artery; 6—ascending aorta; 7—left ventricle; 8—interventricular septum; 9—right pulmonary artery; 10—left pulmonary artery; 11—brachiocephalic artery; 12—left carotid artery; 13—left subclavian artery.

In 2 cases of coarctation of the aorta, satisfactory left anterior oblique and frontal studies were obtained using a rotation from a 45 degree left anterior oblique position to the frontal position.

In 1 case of hypertrophic subaortic stenosis, a rotation from a 45 degree right anterior oblique position to a 45 degree left anterior oblique position was attempted. Satisfactory images were obtained from the right anterior oblique to the frontal plane but the left anterior oblique studies were inadequate due to incomplete filling of the left ventricle at the time rotation had been completed. Stenosis of the pulmonary artery at its bifurcation was well demonstrated in 1 case by using a rotation from the 45 degree right anterior oblique to a 45 degree left anterior oblique position.

In 1 case of complete transposition of the great vessels, separate injections in both ventricles and rotation from the left anterior to the frontal position gave satisfactory lateral, left anterior oblique and frontal views (Fig. 4, *A*, *B* and *C*).

DISCUSSION

In most cases, with the exception of tetralogy of Fallot, rotational multiplane cineangiocardiography has no advantage over the simultaneous biplane method. In fact, the information obtained at the onset and at the end of rotation is not as complete; however, it is satisfactory for diagnostic purposes and in securing the information necessary to the surgeon. As compared to single plane cineangiocardiography, the technique offers several advantages. It is less time consuming and requires only one injection of contrast medium. Nevertheless, the information obtained at separate examinations may in some cases be preferable and worth the time and risks involved.

On the other hand, this technique appears to be superior to other known techniques in the study of tetralogy of Fallot. It permits a precise evaluation of the degree of overriding of the aorta. Complete preoperative studies of a patient with tetralogy of Fallot should demonstrate the right ventricular outflow tract, the ventricular septal defect, the degree of overriding of the aorta, and the size and position of the pulmonary arteries, aorta and subclavian arteries. According to Kjellberg *et al.*[2] at least two projections, the frontal and lateral are required. Abrams and Kaplan[1] prefer using both oblique projections. The lateral and left anterior oblique studies demonstrate the right ventricular outflow tract. The large vessels and subclavian arteries are best visualized in the frontal projection. The degree of overriding of the aorta is evaluated indirectly by the degree of dextroposition and anteroposition of the aorta, best studied in the frontal and lateral plane respectively. The time and degree of opacification of the aorta in relation to that of the pulmonary artery are not reliable signs of overriding because they are also functions of the site of injection in the right ventricle. It is our impression that a more direct means of assessing the degree of overriding is to relate the position of the root of the aorta to that of the interventricular septum. The septum is well visualized as a nonopacified structure only when it is perpendicular to the screen, providing that both ventricles are opacified (Fig. 5, *A*–*C*). The ideal projection which permits a proper view of the septum cannot always be determined beforehand because of the individual variation in its orientation. This plane appears to be somewhere between the left lateral and a 45 degree left anterior oblique position, rendering visualization of the septum possible as it becomes perpendicular to the screen, and thus enabling one to estimate its position in relation to the aorta. This information may help to select patients for surgery, since complete surgical correction is hazardous and difficult whenever overriding is marked.

The experience obtained thus far is too limited to permit definite conclusions. The orientation of the septum and the degree of overriding of the aorta in tetralogy of Fallot are now being studied in this fashion, but with the aid of a marking device in-

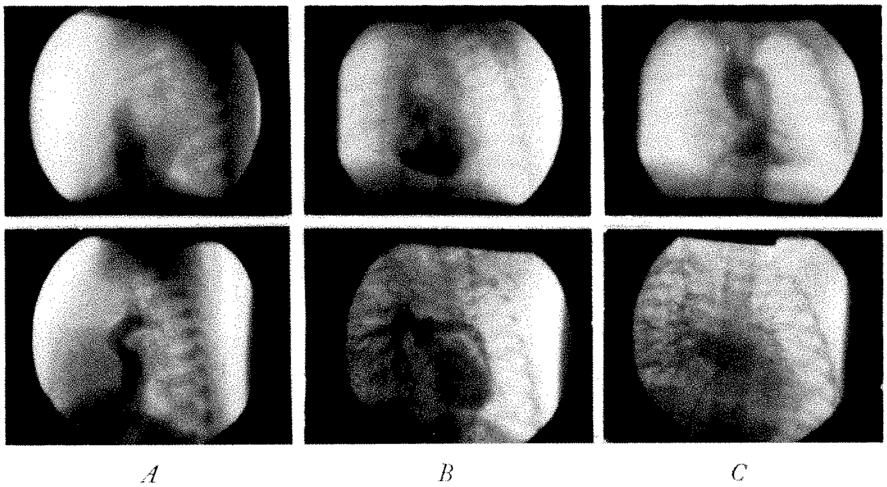

Fig. 4. Single frames of cineangiocardiograms obtained during body rotation from the left lateral to the anteroposterior position in a case of complete transposition.

Top. (*A*) Left lateral, (*B*) left anterior oblique, and (*C*) frontal view, following a single injection of radiopaque substance in the right ventricle. The aorta arises from the right ventricle and the pulmonary artery is not opacified.

Bottom. (*A*, *B* and *C*) Similar projections following a single injection in the left ventricle. The pulmonary artery arises from the left ventricle. *C* shows the pulmonary veins and the left atrium.

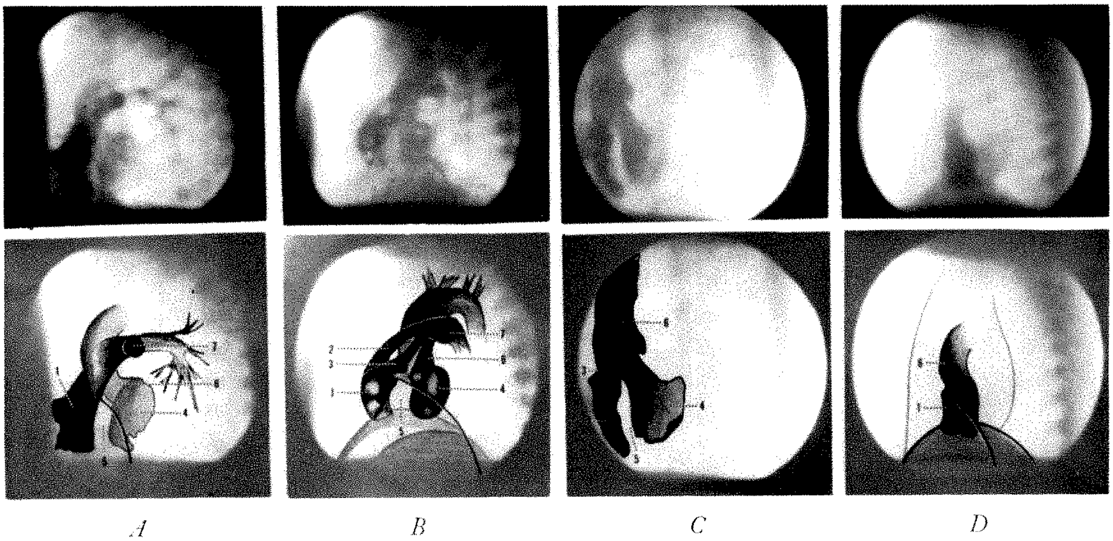

Fig. 5. *Top.* (*A*, *B*, *C* and *D*) Single frames of cineangiocardiograms taken during body rotation following a single injection of radiopaque substance in the right ventricle, showing varying degrees of overriding of the aorta in 3 cases of tetralogy of Fallot and in a case of complete transposition of the great vessels. (*A*) No overriding; (*B*) slight overriding; (*C*) marked overriding; (*D*) aorta arising entirely from the right ventricle in a case of complete transposition. The septum is well visualized in all 3 cases of tetralogy of Fallot.

Bottom. (*A*, *B*, *C* and *D*) Schematic drawings traced from the enlarged cineangiocardiographic image: 1—right ventricle; 2—infundibular stenosis; 3—stream of contrast medium from the right ventricle to the overriding aorta; 4—left ventricle; 5—interventricular septum; 6—ascending aorta; 7—pulmonary artery.

dicating the degree of obliquity during rotation from the lateral to the frontal position. It would also be preferable to have a rotating roentgenographic tube instead of turning the patient. A similar roentgenographic apparatus* is now in use but the rapidity of the tube displacement is not sufficient to permit such a technique.[3]

SUMMARY

A cineangiocardiographic technique whereby multiple successive projections are obtained following a single intracardiac injection of contrast medium is described. This multiplane cineangiocardiography is achieved by rapidly rotating the patient in a 90 degree angle. Both lateral and frontal projections, in addition to the intermediate oblique projections, are thus obtained. The method was found most helpful in the study of tetralogy of Fallot, particularly in evaluating the degree of overriding of the aorta.

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ADDENDUM

This rotational technique was used for coronary arteriography in dogs by FRED S. WINTER and J. STAUFFER LEHMAN. Rotational cinefluorography. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1959, *82*, 120–124.

We wish to thank Dr. Paul David, Director of the Montreal Institute of Cardiology and Doctor Jules Laberge, Chief of the Department of Radiology, Maisonneuve Hospital, for their constructive criticisms. We are indebted to Dr. Ghislaine Gilbert, Head of the Pediatric Section of the Montreal Institute of Cardiology, for the study of these cases. We gratefully acknowledge the assistance of Miss Jacqueline Dupuis, medical artist, Mr. Jean Gauthier, medical photographer, and Mr. Maurice St. Amant, for his technical assistance.

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* The Saturn catheterization table, manufactured by Picker X-Ray Corp., Cleveland 12, Ohio.

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PNEUMOTHORAX AND PNEUMOMEDIASTINUM IN THE NEWBORN*

By CHARLES N. CHASLER, M.D.
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SPONTANEOUS pneumothorax and pneumomediastinum in the newborn have been well described, particularly in the pediatric literature. Since Ruge[13] reported tension pneumothorax in 1878, found at postmortem examination, many other articles on the subject have been published. Davis and Stevens[3] in 1930 reported 6 cases of pneumothorax noted on routine roentgenographic examinations of 702 consecutive newborn infants. No information as to the presence of clinical manifestations was recorded. This is an incidence of approximately 1 per cent. DeCosta[4] found a total of 67 reported cases up to 1940. A review of the English medical literature by Howie and Weed[7] in 1957 revealed 151 cases. These did not include pneumomediastinum and pulmonary interstitial emphysema, when unaccompanied by pneumothorax. Lubchenco[8] reported 27 additional cases of spontaneous pneumothorax—17 or 73 per cent were in premature infants. Recently, Lyon[9] reported 10 cases of pneumomediastinum; the incidence in his series was approximately 1.8 per cent.

It is our purpose to report our experience over a period of 14 years, from 1948 to 1962. During this time approximately 80,000 babies were delivered at Magee-Womens Hospital, Pittsburgh, Pennsylvania. Thirty-six cases of pneumothorax and/or pneumomediastinum were encountered, an incidence of 0.04 per cent. Both of these pathologic entities have been considered together because of the close relationship noted during this study. Of the 36 cases, 50 per cent showed pneumomediastinum alone; 20 per cent showed pneumothorax alone and 30 per cent showed both.

Cases were selected and diagnosed according to the following criteria: (1) Spontaneous pneumothorax: the presence of gas in the pleural spaces without obvious cause of infection, injury or surgery; and (2) pulmonary interstitial and mediastinal emphysema or airblock: extraneous collections of air in the interstitial tissues of the lungs, the mediastinum and their fascial extensions.

CLINICAL DIAGNOSIS

The possibility of the presence of pneumomediastinum and/or pneumothorax should be considered in all infants showing manifestations of respiratory distress at birth. It must be remembered, however, that the infant may appear normal at birth and develop symptoms within 24 to 36 hours. Cases with depressed heart rate during labor, with or without meconium stained fluid, are, in particular, candidates for either pneumomediastinum and/or pneumothorax. Symptoms may vary from a slight increase in respirations to acute desperate dyspnea and cyanosis. The diagnosis is most often suspected by physical signs, and then established by roentgenograms. With pneumothorax the physical signs are: subcostal retraction, decreased or absent breath sounds on the involved side, hyperresonance to percussion and displacement of the heart to the opposite side. With pneumomediastinum, the sternum bulges anteriorly, there is hyperresonance over the sternum and diminished intensity of the heart tones. Hammon's sound may be present; this is a crackling sound heard synchronously with the heart beat.

ROENTGEN FINDINGS

Pneumothorax may exist alone, either unilaterally or bilaterally. Such a diagnosis is usually easily made. The radiolucent air

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* Presented at the Sixty-fourth Annual Meeting of the American Roentgen Ray Society, Montreal, Quebec, Canada, October 8–11, 1963.

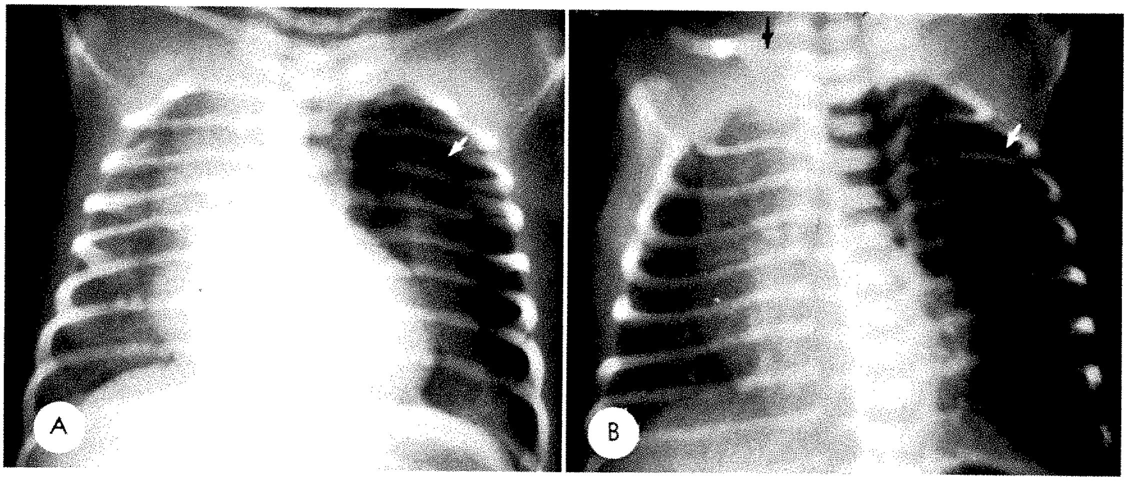

FIG. 1. (*A*) Extensive left pneumothorax (arrow) with displacement of mediastinal contents to the right. (*B*) Fourteen hours later. Pneumothorax improved (identical arrow), right lung well expanded. The top arrow shows evidence of rotation of infant causing spurious shift of mediastinal contents to right.

space without lung markings may be clearly visible, although an overexposed roentgenogram will completely obliterate free air. Mediastinal structures may be shifted to the opposite side; however, this is not necessarily a concomitant finding (Fig. 1, *A* and *B*). A roentgenogram taken in deep expiration usually accentuates the degree of collapse of the involved side. The lung may herniate across the mediastinum. The vessels of the opposite lung may be engorged. Certain definite pitfalls do occur in the roentgen diagnosis of pneumothorax. Skin folds in the axillary areas (Fig. 2) or the overlying scapula (Fig. 3) may resemble a pneumothorax The vertical fissure line described by Davis[2] along the right lower lateral hemithorax could be misinterpreted as a small pneumothorax (Fig. 4). Slight rotation of the chest can easily obscure a minimal degree of pneumothorax.

Pneumothorax may be combined with mediastinal emphysema (Fig. 5, *A* and *B*). In such cases one or several of the above listed criteria may be present plus additional evidence of pneumomediastinum. Such evidence may be detected in both the anteroposterior and lateral projections. In the frontal projection the heart is outlined by air and its border may be sharper. The lobes of the thymus may be shifted giving

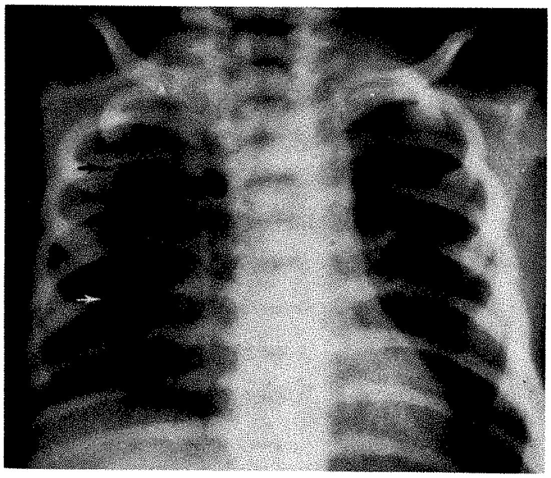

FIG. 2. Possible error in diagnosis—skin fold in axillary area (arrows).

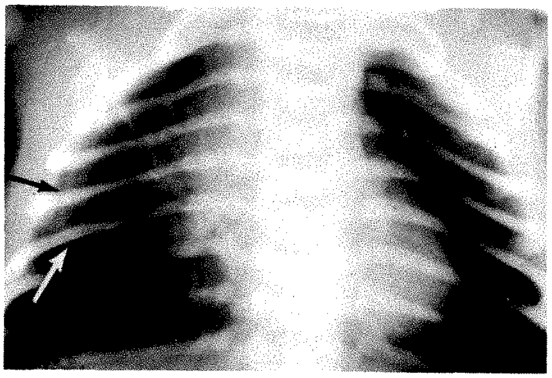

FIG. 3. Possible error in diagnosis—overlying scapula (arrows).

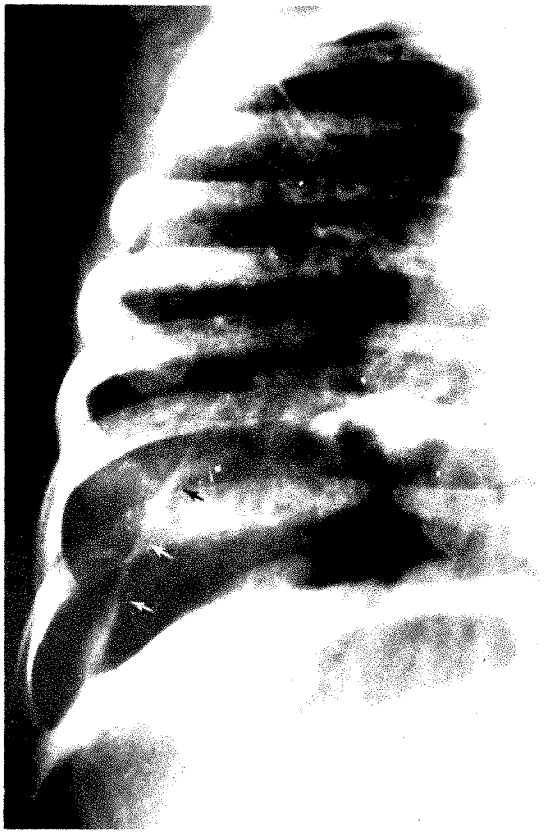

FIG. 4. Possible error in diagnosis—vertical fissure line (Davis) (arrows).

the "spinnaker sail" sign described by Caffey[1] and Moseley.[12] The mediastinal air column outlines the medial borders of the lungs and lateral margins of the heart and thymus. The thoracic vertebral column is better delineated (Fig. 6). The lateral view may reveal small collections of air in the anterior mediastinum that cannot be recognized in other projections. The sternum may be elevated anteriorly and may bulge forward to a marked degree, depending on the amount of air collected in the space and depending on whether the air can escape into the soft tissues of the neck or abdomen (Fig. 7). Air may be seen dissecting into the soft tissues of the neck (Fig. 8, *A* and *B*). It also may dissect into the pericardium, to the peritoneum, to the groin and leg and into the connective tissues of the arm, head, chest and abdomen. In difficult cases, an oblique roentgenogram may show air between the heart and thymus.

Air loculated behind the sternum must be differentiated from physiologic and anatomic structures. In this view, air in the pleural space, air in the mediastinum, air in distended lung, and loculated pneumopericardium all have the same appearance. Usually, loculated air in the anterior mediastinum is located in a higher position and may migrate upwards when the subject is in the erect posture. At times there is a fortuitous arrangement of shadows simulating loculated air. The cartilaginous ends of the ribs must not be interpreted as air. The lateral view may also be misleading if pneumothorax is present under tension, or if

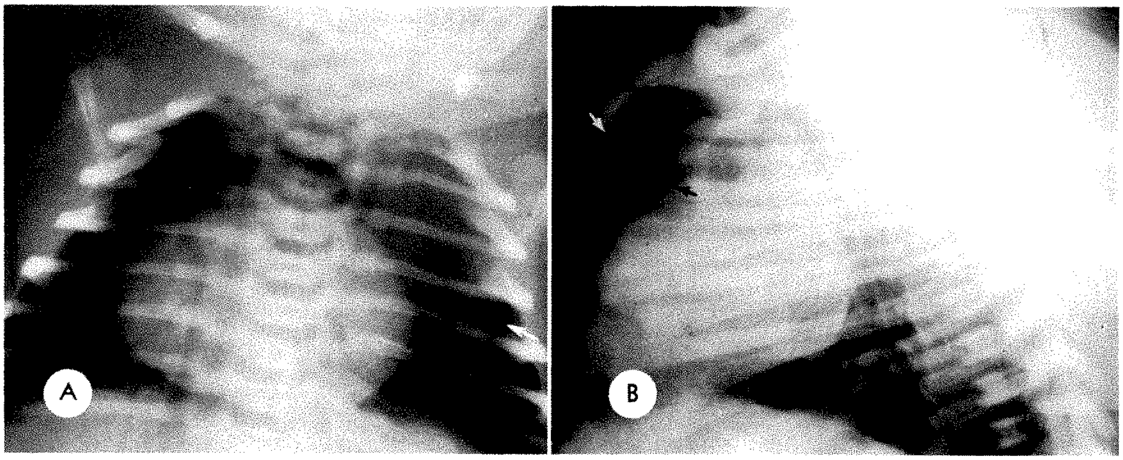

FIG. 5. Pneumothorax may be combined with mediastinal emphysema. (*A*) Frontal view. Arrow points to collapsed left lung. (*B*) Lateral view. Mediastinal air bulges sternum anteriorly (arrows).

there is herniation of the anterior mediastinum by an emphysematous lung. A true lateral view is extremely important in establishing the presence of a pneumomediastinum. As so vividly described by Lyon,[9] the direct lateral roentgenogram demonstrates the sternal bones within the soft tissue shadow of the chest wall. Slight rotation projects the radiolucent anterior lung of the contralateral side forward and it will be seen anterior to the sternal ossification centers, thus resembling a pneumomediastinum. Examination of the vertebral column and posterior rib cage will confirm this rotation of the thorax.

RESULTS

The most striking feature of this survey is the large number of abnormal labors and deliveries often conducive to fetal distress (Table I). Twenty-nine of the 36 babies had definite evidence of obstetrical complications. This brings up the question whether, because these infants were compromised, they required resuscitative efforts which contributed to the development of pneumothorax or pneumomediastinum? On careful review of the charts, however, only 7 cases had mechanical or artificial respiration recorded; the rest presumably breathed without assistance.

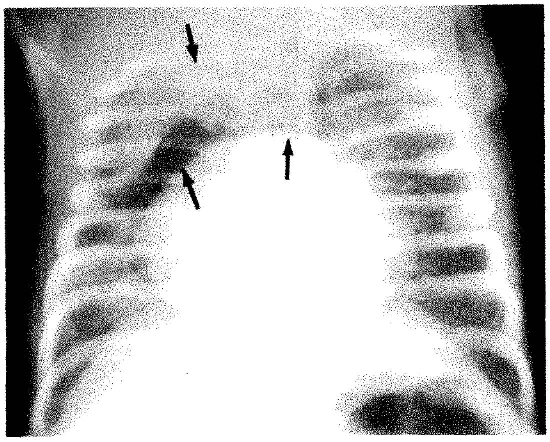

FIG. 6. Pneumomediastinum. Frontal projection. The heart is outlined by air and its border is sharper (lower left arrow). The lobes of the thymus shifted giving the "spinnaker sail" sign described by Caffey and Moseley (upper arrow). The thoracic vertebral column is better delineated (lower right arrow).

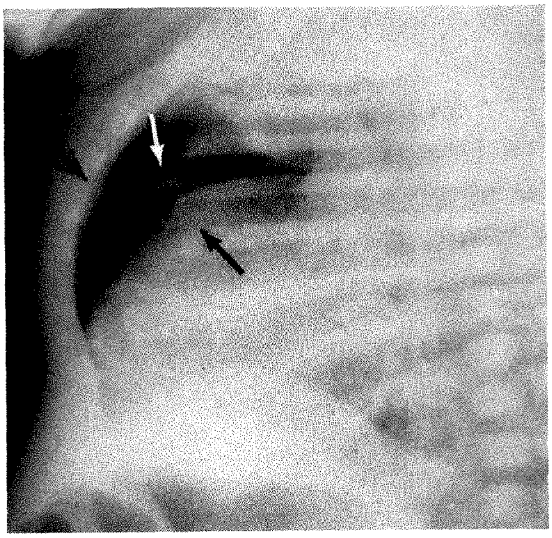

FIG. 7. Pneumomediastinum. Lateral view. Air outlines thymus (right arrows); sternum bulges anteriorly (left arrow).

Twenty of the 36 cases in our series had immediate outright respiratory distress (Table II). Nine presented minimal manifestations detected clinically at birth. Five infants developed positive evidence within 24 to 36 hours. Two cases presented no detectable clinical manifestations at any time. Cyanosis was noted in 19 infants; this

TABLE I

OBSTETRICAL HISTORY

Operative Deliveries			16
Mid forceps		8	
Breech extraction		2	
Internal podalic version		1	
Cesarean section		5	
Placenta previa	1		
Cephalopelvic disproportion	1		
Infection	1		
Fetal distress	2		
Spontaneous Deliveries			20
Precipitous labor		4	
Postmature		5	
Nuchal cord		4	
Normal		7	

consisted of either generalized cyanosis or limited involvement of the lips and extremities. Meconium stained secretion was aspirated from the air passages in 14 cases. Respiratory difficulty, ranging from no respirations for a period of 20 minutes to mild involvement was noted. Respirations were rapid and shallow and at times respiratory movement was confined to one side, as in unilateral pneumothorax.

Discrepancies in heart tones occurred often. Actual displacement with pneumothorax was found in 5 cases. Distant heart tones were observed in 13 infants. The intensity and location of heart tones varied with the amount and distribution of accumulated air. Hammon's sound was only recognized once by a clinician.

A statistical summary of the cases is given in Table III and of the pathologic entities encountered in Table IV.

DISCUSSION

Pneumothorax and/or pneumomediastinum occurs more often than is suspected in the newborn infant. Many cases are undoubtedly never diagnosed because complete roentgenographic study cannot be done. Many infants may not present sufficient manifestations on which to make a clinical diagnosis or to warrant a roentgenographic study to confirm such an impression. The incidence of pneumothorax of the newborn today is probably close to the 0.07 per cent reported by Harris and Steinberg.[6] The fact that Davis and Stevens[3] detected 6 cases of pneumothorax on routine infant roentgenograms makes one wonder how many cases may be missed. However, the possibility of errors in diagnosis must be considered so that the incidence may be slightly lower. At that time, skin folds, etc., may have been misinterpreted as pneumothorax. Moreover, as Lubchenco[8] has shown, pneumothorax may occur as long as 44 days after birth and this fact may affect the incidence.

As noted in Table II, many predisposing factors may exist. However, in the majority of cases, the exact cause is unknown. Two mechanisms must be kept in mind in the understanding of causal agents en-

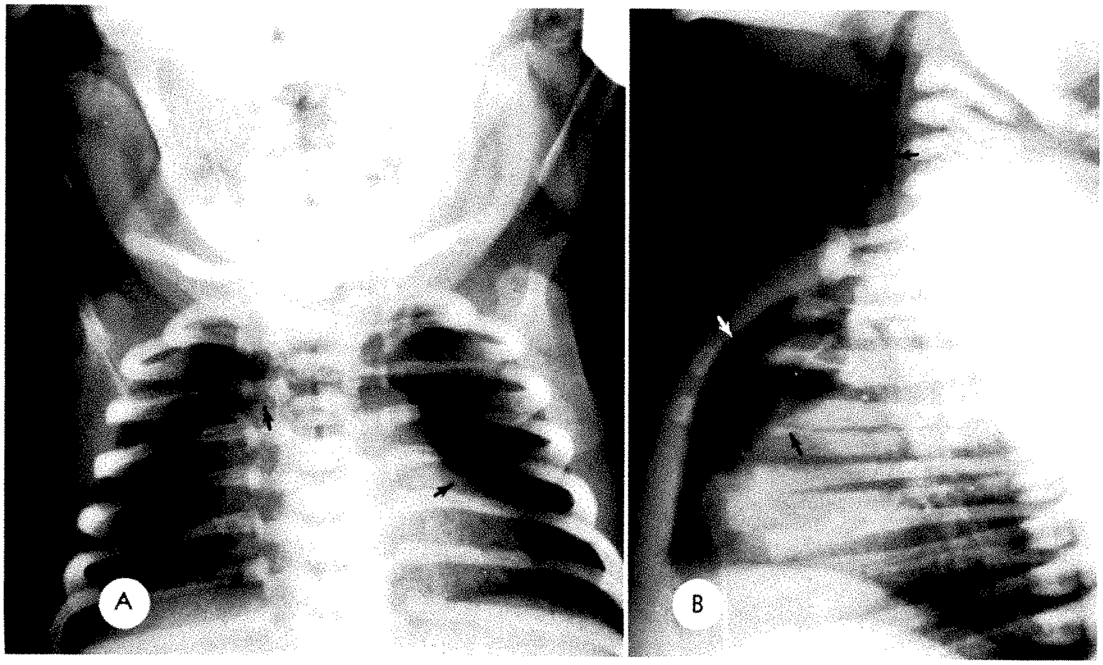

Fig. 8. Pneumomediastinum with dissection of air into the soft tissues of the neck. (*A*) Frontal view shows the sharp borders of the heart (arrows) and radiolucency over the upper thoracic spine. (*B*) In the lateral projection the sternum bulges anteriorly (left arrow) and the thymus is elevated. The 2 arrows on the right indicate the extent of dissection.

TABLE II

CASE SUMMARIES OF 36 NEWBORNS WITH SPONTANEOUS PNEUMOTHORAX AND/OR PNEUMOMEDIASTINUM (MAGEE-WOMENS HOSPITAL 1948–1962)

No.	Weight (gm.)	Color Sex	Delivery	Condition at Birth	Diagnosis	Treatment	Termination	Resuscitation and Remarks
1	3,590	W-M	Mid forceps, nuchal loop, 31 hours	Meconium, intense cyanosis, cried several times, then quit	Pneumothorax, right—pneumomediastinum	Conservative, aspiration, oxygen	Improved	Aspiration of mucus, none
2	3,125	W-M	Low forceps, primary, uterine inertia, ruptured membranes	Cyanosis of extremities despite oxygen, respiratory difficulty with poor cry	Pneumothorax left	Oxygen, antibiotics	Improved	None
3	2,690	W-F	Normal OA, spontaneous, induced labor	Spontaneous respiration, weak cry, heart tones distant, shallow breath, sounds poor	Pneumothorax, left	Oxygen, penicillin	Improved	None
4	3,315	W-M	Elderly primipara, cesarean section, hypertension, cephalopelvic disproportion	Meconium stained fluid, difficult resuscitation, fetal distress, no breath sounds on right	Pneumothorax, right—pneumomediastinum	Needle in mediastinum, oxygen, penicillin	Expired	No autopsy, difficult resuscitation, bronchoscopy negative
5	2,640	W-M	41 weeks, cesarean section due to fetal distress	True knot on cord, fetal distress, respiration delayed 5 minutes, meconium stained vernix, generalized cyanosis, marked symptoms postmaturity	Pneumothorax, bilateral—pneumomediastinum	Oxygen	Expired, at autopsy-air in mediastinum, interstitial emphysema of mediastinum and lungs	Mechanical resuscitation, laryngoscopy aspiration of bright red mucus
6	2,700	W-F	Primigravida, traumatic decomposition, heavy medication	Cyanosis	Pneumothorax, left	Artificial respiration	Improved	Artificial respiration
7	2,403 (second twin)	W-M	RH positive, twins, int. podalic version and extraction, premature labor, premature rupture of membranes	No respiration for 20 minutes, much mucus, asphyxia livida	Pneumothorax, left	Oxygen, aspiration	Improved	Associated imperforate anus, hemivertebrae, artificial respiration and aspiration
8	4,165	W-M	Low transverse arrest, mid forceps, age 40, gravida III	Spontaneous respirations, asphyxia livida-cyanosis, heart sounds distant and to right of sternum	Pneumothorax	Oxygen	Improved	None
9	3,225	W-F	LOA, low forceps, age 44, postmature	Meconium, limp, rapid shallow respiration, no cyanosis	Pneumomediastinum	Caffein, oxygen	Improved	No artificial respiration, gastric lavage, large amounts of green fluid
10	2,850	W-F	OA, spontaneous	Shallow respiration, good cry, no asphyxia, in 2 days cyanosis and shallow respirations	Pneumomediastinum	Oxygen	Improved, hepatitis	None
11	3,585	W-M	ROA-OA, low forceps, 44 weeks, postmature, precipitous labor	Long green cord, almost gangrenous	Pneumomediastinum	Oxygen	Improved	None
12	3,290	W-F	Low forceps, normal delivery	Asphyxia livida, fetal distress, loops of cord-short cord, heart tones distant, respiration delayed 5 minutes	Pneumomediastinum	Oxygen	Improved	Artificial respiration
13	3,705	W-M	ROP, rotation, mid forceps, traumatic delivery	Mild cyanosis, normal at 12 hours	Pneumomediastinum	Oxygen	Improved	None
14	2,895	W-F	ROP-OA, mid forceps	Mild cyanosis-2 plus over entire body on crying, heart sounds distant, liver down	Pneumothorax, left—pneumomediastinum	Oxygen	Improved	None
15	3,710	W-M	LOP, mid forceps, rotation, cephalopelvic disproportion	Aspirated meconium, substernal and suprasternal retraction	Pneumomediastinum	Oxygen, penicillin	Improved	None
16	3,990	W-M	LOA, low forceps	Baby flaccid, cyanotic, asphyxia livida, respiratory distress, narcosis-mucus aspiration	Pneumothorax, bilateral—pneumomediastinum	Oxygen, penicillin, streptomycin	Death	Congenital anomaly of kidney and bladder, terminal pneumonia
17	3,925	W-M	LOP-OA, mid forceps, age 41, 19 yr. history of sterility	Limp, cyanotic, fetal distress, meconium in nose and throat, feeble cry, asphyxia livida, meconium	Pneumomediastinum	Oxygen, penicillin	Improved	Mongolism, none, aspiration from nose, throat and stomach.
18	4,145	W-F	LOA-OA, spontaneous, 44 weeks, postmature, pre-eclampsia, positive serology, heavily medicated, no prenatal care	Respiration delayed 5 minutes, cyanosis, fine rales, hyperresonant chest	Pneumothorax, bilateral—pneumomediastinum	Oxygen	Death, autopsy-hyaline membrane disease, 4+ serology	Aspiration from nasopharynx and stomach, air aspirated from mediastinum, artificial respiration

TABLE II (*Continued*)

No.	Weight (gm.)	Color Sex	Delivery	Condition at Birth	Diagnosis	Treatment	Termination	Resuscitation and Remarks
19	3,240	W-M	LOA, low forceps	Spontaneous cry, heart sounds louder on right, no cyanosis early, later slight peripheral cyanosis	Pneumothorax, left	Oxygen	Improved	None
20	3,640	W-M	Breech, amnionitis, uterine dystocia, cesarean section	One breath at 1 minute, then limp and flaccid for 4–5 minutes, respiratory difficulty, no cyanosis, sternal retraction	Pneumomediastinum	Oxygen, penicillin	Improved	None
21	3,440	W-F	Precipitous labor	Much mucus in mouth and nose, moderate generalized cyanosis with retraction, dyspnea, 140 heart rate	Pneumomediastinum	Oxygen	Improved	Jaundice, none
22	2,780	W-M	LST, frank breech, primary uterine inertia, 3 weeks premature, membranes ruptured for 2 days	Cried spontaneously, normal at birth, distress 17 hours later, decreased sounds in right apex	Pneumomediastinum	Oxygen	Improved	None
23	2,285	W-F	LOT-OA, mid forceps, heavy medication, postmature by date and appearance	Respiratory distress at birth, heart sounds on right, color good with slight cyanosis of hands and feet plus meconium	Pneumothorax, left—pneumomediastinum	Oxygen, penicillin. streptomycin	Improved	None
24	2,750	W-M	Twins; LOA, low forceps, mild preeclampsia	Heart tones on right side, no murmurs, lungs clear, true knot? heart sounds "tappy"	Pneumothorax, left	Oxygen	Improved	None
25	3,305	W-M	LOA, low forceps, postmaturity	Good cry and color, systolic murmur, EKG-possible right ventricular strain	Pneumomediastinum	Oxygen	Improved	None
26	3,060	W-M	Cesarean section, full term, contracted pelvis, meconium, transverse lie, placenta previa with bleeding	Thick meconium at birth, distant heart sounds, positive pressure for 20 minutes, retraction, did not breathe for 20 minutes, respiratory distress since birth, aspirated mucus, crepitant lungs, two loops around neck-tight	Pneumomediastinum	Oxygen	Improved	Artificial respiration, endotracheal intubation suction
27	3,590	W-F	LOA, low forceps	Spontaneous respirations, cry good, physical examination negative, no symptoms	Pneumomediastinum		Improved	None
28	2,705	W-F	Normal delivery	Breath sounds suppressed in left chest, heart tones distant, no cyanosis at birth	Pneumothorax, left—pneumomediastinum		Improved	None
29	3,675	W-M	Frank breech, RSA, cesarean section, inertia of labor, premature rupture of membranes-26 hours	Slow to breathe spontaneously, no cyanosis, heart sounds distant	Pneumothorax, right—pneumomediastinum	Oxygen	Improved	None
30	3,065	W-M	LOT-OA	Spontaneous respirations, poor color, slightly cyanotic, distant heart sounds, much mucus	Pneumothorax, right—pneumomediastinum	Oxygen	Improved	None
31	2,945	N-M	Postmature	Meconium stained, no cyanosis, chest retraction	Pneumomediastinum	Oxygen	Improved	None
32	3,625	W-M	LOA, mid forceps	No respiratory distress immediately, slight cyanosis later, distant heart sounds, grunting respirations	Pneumomediastinum	Oxygen, suction	Improved	None
33	2,710	W-F	Prolonged labor, low forceps, postmature, heavily medicated	Fetal anoxia, respirations delayed 1 minute, meconium stained, cyanotic, distant heart sounds	Pneumomediastinum	Oxygen	Improved	Bag breathing, artificial respiration, needle aspiration of 70 cc. air
34	2,985	W-M	Normal delivery	Respirations delayed 2 minutes, cyanotic at birth, distant heart sounds, chest hyperresonant	Pneumomediastinum	Oxygen	Improved	Stomach aspirated
35	3,100	N-F	No prenatal care, abruptio placentae, nuchal cord	Prominent sternum, mucus stained, apnea 2–3 minutes	Pneumomediastinum	Oxygen, bag and mask	Improved	Artificial respiration
36	3,090	N-M	Low forceps	Cyanosis, cry spontaneous but weak, resuscitation, slight expiration grunt, minimal subcostal retraction, displaced heart sounds	Pneumothorax, left—pneumomediastinum	Oxygen, artificial respiration mouth to tube, air aspirated from pleural space	Death	Multiple congenital anomalies, hyaline membrane disease

countered clinically. First, pathologic processes of the respiratory parenchyma and, secondly, mechanically induced overventilation or distention of the alveoli. Either or both of these may result in weakening of the walls of the respiratory tract and contribute to a break in the continuity of its wall. In pneumothorax of the newborn infant due to congenital deformities of the respiratory system, local trauma, or neonatal infections, the pathologic lesion is the more important. However, in labored respirations, secondary to obstruction due to tenacious secretions in the bronchial tree, overdistention plays a causal role.

The probable explanation of the genesis of spontaneous mediastinal emphysema is contained in a series of experiments performed by Macklin and Macklin.[10,11] By artificially increasing the intrapulmonary pressure in a lobe of the lung of cats and other animals, they were able to demonstrate that the air enters the perivascular sheaths of the finer branches of the pulmonary vessels, presumably through the numerous minute ruptures in the walls of the alveoli. As the increased intrapulmonary pressure continues, the small bubbles of air coalesce into large ones as they move toward the root of the lung through the artifically produced channels in the vascular sheaths. At the root of the lung, the air bubbles may merge into large blebs which can impede pulmonary circulation. Further leakage causes these blebs to break through into the mediastinum. The air in the perivascular sheaths may extend into the adjoining connective tissue and dissect a pathway toward the pleura where it may form a subpleural bleb, particularly in the region of the root of the lung. Rupture of this bleb may produce a pneumothorax.

Table III

STATISTICAL SUMMARY

Males	23
Females	13
White	33
Negro	3
Private	33
Ward	3
Premature	None? (1 twin)
Twins	2
Postmature	8
Artificial respiration	7
Deaths	5
Pneumothorax bilateral—pneumomediastinum	3
Pneumothorax, right—pneumomediastinum	1
Pneumothorax, left—pneumomediastinum	1
Weight	
Over 4,000 gm	2
3,500–4,000 gm	10
3,000–3,500 gm	11
2,500–3,000 gm	11
2,000–2,500 gm	2 (1 twin) (1 postmature)

Table IV

PATHOLOGIC ENTITIES

Pneumothorax, right	0
Pneumothorax, left	7
Pneumothorax, bilateral	0
Pneumomediastinum	18
Pneumothorax, bilateral—pneumomediastinum	3
Pneumothorax, left—pneumomediastinum	4
Pneumothorax, right—pneumomediastinum	4
Pneumomediastinum with neck dissection	4
Pneumothorax, unilateral—pneumomediastinum with neck dissection	1
Pneumothorax, bilateral—pneumomediastinum with neck dissection	1
Hyaline membrane disease (autopsy study)	3

The paths of extension of air in the mediastinum are as follows: The air tends to follow with predilection the fascial planes, particularly the sheaths surrounding blood vessels. It may spread upward into the root of the neck, the face, axilla, anterior chest wall and arms. It is possible for it to dissect up along the sides of the trachea to the floor of the mouth, extending under the base of the tongue which becomes elevated. It may extend forward between the parietal pleura and pericardium to appear as blebs overlying the heart, laterally into the opposite lung and downward into the retroperitoneal space where it may outline the kidneys, ureters and renal vessels. Hamman[5] suggests that rupture of air from the mediastinum into the pleural cavity is a possible explanation as to why, in some cases, the development of benign pneumothorax may be beneficial. By collapsing the lung the pneumothorax stops further leakage of air into the vascular sheaths, relieves the pressure on the mediastinal structures and frees the circulation in the lungs.

Recently, Ziegler[14] postulated that idiopathic spontaneous pneumothorax may have a familial tendency and is probably transmitted by a dominant autosomal gene. This was based on case histories of 8 patients.

TREATMENT

Treatment of the condition depends on the severity of the symptoms. If manifestations are minimal, no treatment is necessary. Gentle suction may be used to clear the air passages. Oxygen may be indicated to relieve dyspnea and cyanosis. Prognosis is usually excellent; but in the event of severe symptoms, aspiration of the mediastinum is advisable. Air may be present in loculated bubbles so that cautious exploration is necessary. Antibiotic therapy may be used. Thoracotomy or aspiration may be necessary in patients with tension pneumomediastinum. If air dissects up into the neck, the tissue serves as a safety valve. If it ruptures into the pleura, a pneumothorax develops and treatment is difficult. Evidence of increasing or tension pneumothorax may require thoracentesis and continuous drainage by way of an underwater tap.

SUMMARY

1. From 1948 to 1962 approximately 80,000 babies were delivered at Magee-Womens Hospital, Pittsburgh, Pennsylvania. A review of all roentgenograms for the evaluation of respiratory distress in these babies shows 36 cases of pneumothorax and/or pneumomediastinum—an incidence of 0.04 per cent.

2. Pneumothorax and pneumomediastinum must be considered in all infants showing manifestations of respiratory distress at birth.

3. Usually, there is a history of a definite obstetrical problem. Twenty-nine of the 36 babies had definite evidence of obstetrical complications.

4. Signs and symptoms are present and must be recognized—cyanosis, meconium, respiratory difficulty and especially impaired heart tones, either distant or displaced. Twenty of the 36 cases had outright respiratory distress. Nine presented minimal manifestations detected clinically at birth. Five infants developed positive evidence within 24 to 36 hours.

5. Roentgen criteria: (a) The diagnosis of pneumothorax is not difficult. The radiolucent air space without lung markings may be clearly visible. The opposite lung shows impaired aeration. The vessels of the opposite lung may be engorged. The mediastinal structures may or may not be shifted to the opposite side. A roentgenogram taken in deep expiration accentuates the degree of collapse of the involved side. (b) Pneumomediastinum presents more of a problem; follow-up roentgenograms, oblique views, horizontal and erect positioning may be necessary. In the frontal projection the heart and lobes of the thymus may be distinctly outlined by air. A lobe of the thymus may be shifted giving the "spinnaker sail" sign described by Caffey and Moseley. The thoracic vertebral column is better delineated. A true lateral view is imperative. The sternum may be elevated and may bulge forward to a marked degree depending on the amount of air collected in the retrosternal space. There is retrodisplacement of the mediastinal contents. The thymus may be elevated and sharply delineated. Retropharyngeal soft tissue air dissection may be noted.

6. Pneumothorax and pneumomediastinum often occur concomitantly. Our series revealed 50 per cent pneumomediastinum, 20 per cent pneumothorax alone, and 30 per cent combined.

7. Differential diagnosis: (a) Pneumothorax must be differentiated from skin folds, the overlying scapula and the vertical fissure line of Davis. An overexposed roentgenogram may completely obscure free air. (b) As regards pneumomediastinum, a radiolucent anterior retrosternal

space does not necessarily indicate free air. Other physiologic and anatomic structures must be considered. In the lateral view, air in the pleural space, air in the mediastinum, air in distended lung and loculated pneumopericardium all have the same appearance.

8. Treatment depends on the severity of the symptoms. If manifestations are minimal, no treatment is necessary. Gentle suction to clear the air passages, oxygen and antibiotic therapy may suffice. If symptoms become severe, we must be prepared to recommend aspiration. For a pneumothorax under tension, thoracentesis and continuous drainage by way of an underwater tap may be necessary.

CONCLUSIONS

Pneumothorax and/or pneumomediastinum must be considered in all infants presenting manifestations of respiratory distress at birth. The incidence in our 14 year period of observation was 0.04 per cent. An obstetrical complication is often present. The diagnosis is first suspected clinically and then may be confirmed roentgenologically. The roentgen diagnosis of pneumothorax is not difficult. The diagnosis of pneumomediastinum presents a slightly more complex problem. Treatment is usually supportive, although aspiration and thoracentesis may be necessary.

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MEASLES PNEUMONIA IN AN ADULT*

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THE roentgenographic findings in the chest in cases of childhood rubeola have been described in detail.[1,2,4–7,9,11–14] This disease is much less frequent in the adult but it does occur. In 1955, Pegni[10] reported 64 cases of adult measles in a military base but the chest roentgen findings were not described and the exact diagnosis was uncertain. A review of the literature revealed no specific reports of roentgenographic findings in adults with rubeola.

Abnormalities of the chest in rubeola can be observed in two separate systems: (1) pulmonary, and (2) reticuloendothelial. These systems are involved independently of each other.

Roentgenographically, the pulmonary changes vary from slight pleural reaction to massive consolidation and atelectasis involving any or all lobes, but having a predilection for the lower lobes.[2] The incidence of pulmonary infiltration varied from 25 per cent[13] to 77 per cent.[11]

The reticuloendothelial system exhibits moderate to massive hilar and mediastinal lymph node enlargement with variable lymphogenous accentuation. The incidence of this finding varied from 64 per cent[2] to nearly 100 per cent.[12]

Immune serum[7] and antibiotics[11] may alter and decrease the pulmonary findings and complications, but have no effect on the hilar lymphadenopathy.

The lymph node enlargement reaches a peak at the time of the rash eruption and regresses shortly thereafter. The pulmonary infiltration appears in the late prodromal stage or in the early stage of rash eruption. Eighty per cent of the patients who develop pulmonary infiltration do so before or at the time of the rash eruption.[12] The pulmonary infiltration may persist and progress after the rash has disappeared.

The lymph node enlargement regresses during the exanthematous stage and before the pulmonary changes clear up. Both the reticuloendothelial and pulmonary changes usually disappear within 6 to 10 months.[4]

In cases which prove to be fatal the pulmonary infiltration persists and progresses while the lymph nodes return to normal size.

The following case is reported as representative of the usual course of rubeola in an adult.

REPORT OF A CASE

A 31 year old man was admitted to the North Carolina Baptist Hospital on January 5, 1962 with the chief complaint of a cold. Ten days prior to admission he noted mild rhinorrhea and 6 days later developed a dry cough, chills, fever, malaise, nausea, vomiting and diarrhea. He received penicillin and cough medicine from his physician without relief. Although unable to retain food or liquids for 3 days, he continued to have up to 6 watery bowel movements per day. No myalgia, dyspnea, chest pain or hemoptysis was present.

The temperature was 102°F., the pulse 84 and the respirations 26. The blood pressure was 122 systolic and 80 diastolic. An erythematous, maculopapular rash was noted over his face, thorax, abdomen, buttocks and proximal extremities. The palms and soles were uninvolved. He stated that the rash had appeared the day of admission.

Several small, nontender cervical and axillary lymph nodes were found. The conjunctiva and mucous membranes were injected and typical Koplik's spots were noted on the buccal mucosa by the pediatric consultant.

Crepitant rales were heard in both lung bases. There was no demonstrable organomegaly. A neurologic examination was normal. The patient gave no history of being exposed to measles.

Urinalysis was normal. Examination of the blood revealed a hemoglobin of 13.8 gm. per 100

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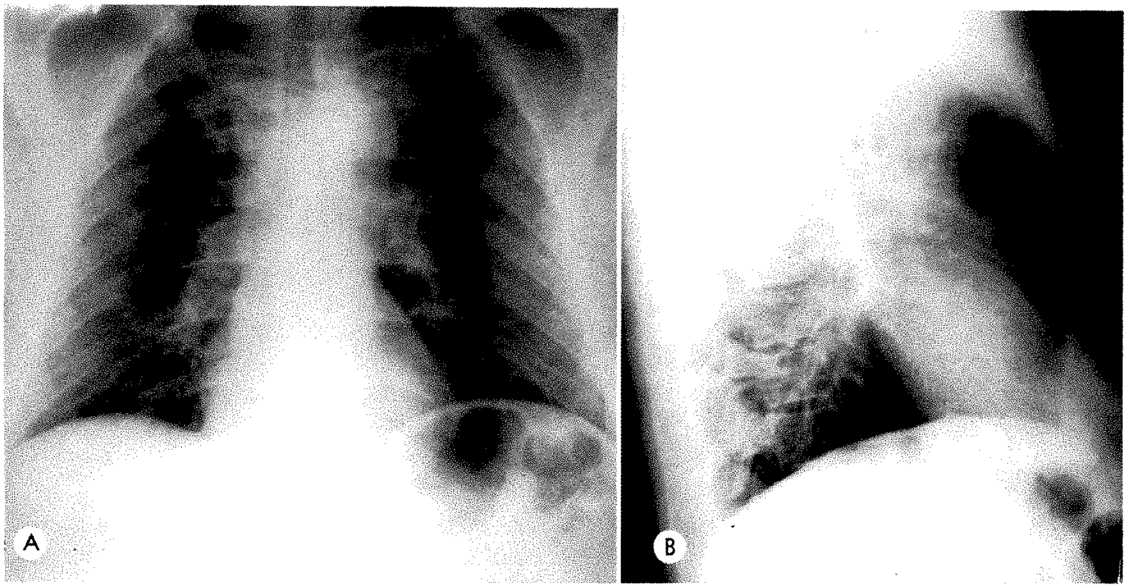

Fig. 1. (*A*) Posteroanterior and (*B*) lateral roentgenograms of the chest showing massive mediastinal and hilar lymphadenopathy, marked lymphogenous accentuation and bilateral basilar pulmonary infiltration.

ml. and a white blood cell count of 3,600 with a differential of 64 segmented neutrophils, 23 band neutrophils, 10 lymphocytes and 3 monocytes. Blood and serum chemistries were normal. Stool and throat cultures showed a normal flora. Cold and febrile agglutinins were normal. The heterophile antibody titer was normal.

Roentgenograms of the chest (Fig. 1, *A* and *B*) showed bilateral hilar lymphadenopathy with lymphogenous accentuation and an infiltration in both lower lung fields.

The patient was given fluids and supportive care. He received no antibiotics. By the third hospital day his temperature was normal. At that time the rash was diminishing but also spreading to his arms, back and dorsa of the feet. He continued to improve and was discharged on the fifth hospital day. A repeat

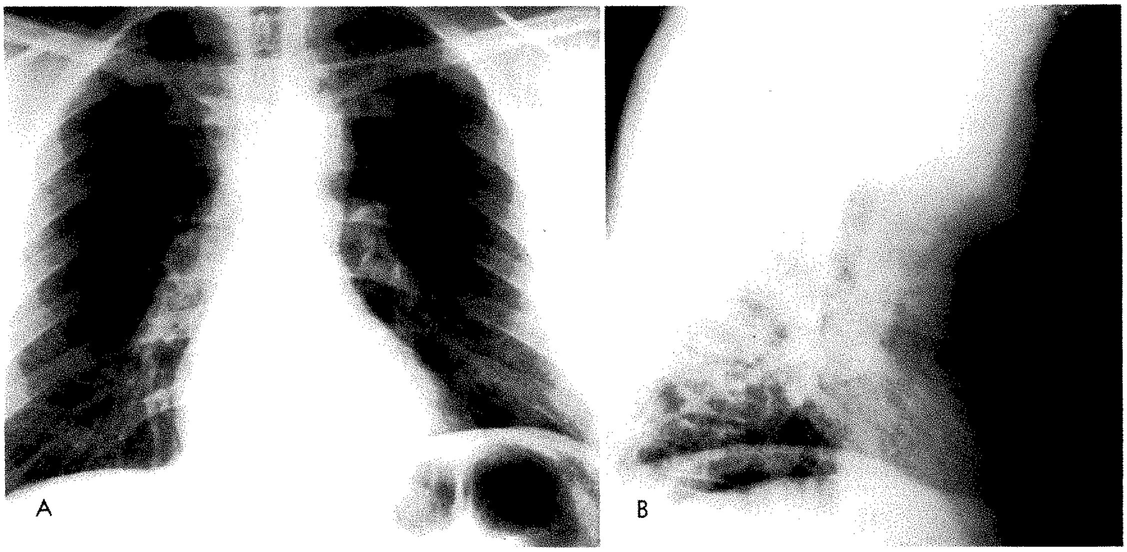

Fig. 2. (*A*) Posteroanterior and (*B*) lateral roentgenograms of the chest made 4 days after Figure 1, *A* and *B*, showing dramatic reduction in the lymphadenopathy, disappearance of the lymphogenous accentuation and an improvement in basilar infiltration.

white blood cell count at that time was 9,200.

Chest roentgenograms (Fig. 2, *A* and *B*) 4 days after admission showed considerable diminution of the hilar and mediastinal lymphadenopathy and a clearing of the lymphogenous accentuation in addition to improvement in the basilar infiltration.

The patient was seen 3 months later. He was asymptomatic. A serum sample was taken and sent, along with his admission serum, to the state laboratory for virus studies. It was diagnostic of measles and adenovirus infection.

Chest roentgenograms taken at that time (Fig. 3, *A* and *B*) showed slight residual lymph node enlargement and minimal accentuation of the basilar lung markings.

DISCUSSION

Measles infection in humans results in formation of two types of giant cells: (1) Warthin-Finkeldey giant cells, and (2) syncytial epithelial giant cells.[3]

The Warthin-Finkeldey giant cells are found in lymph nodes throughout the reticuloendothelial system and are considered diagnostic of rubeola. They are found during the prodromal stage of measles and disappear soon after the onset of the rash.

Syncytial epithelial giant cells are found in the epithelium of the lower respiratory tract. Interstitial pneumonitis in association with these giant cells constitutes the chief morphologic criterion of giant cell pneumonia.

The syncytial epithelial giant cells appear in tissue culture of many viruses including varicella, herpes zoster, herpes simplex, measles, distemper and a variety of adenoviruses, but the ability to produce this giant cell reaction in the lower respiratory tract appears to be a specific feature of measles. The measles virus is the only organism which has been isolated to date in cases of true giant cell pneumonia in humans.

There was a recent case report of fatal giant cell pneumonia in a questionable case of measles.[8] The patient was a 34 year old female who was diagnosed and successfully treated for lymphosarcoma several years before her final admission. One month prior to her death she developed severe and progressing dyspnea. At necropsy the hilar lymph nodes were normal in size but demonstrated inflammatory hyperplasia. The pulmonary findings were typical of giant cell (syncytial) pneumonia. The patient had developed sore eyes, a transient rash and a pyrexic illness 1 month prior to death. This may be a case of atypical measles with progression of the pulmonary infiltration and regression of the hilar lymph node enlargement.

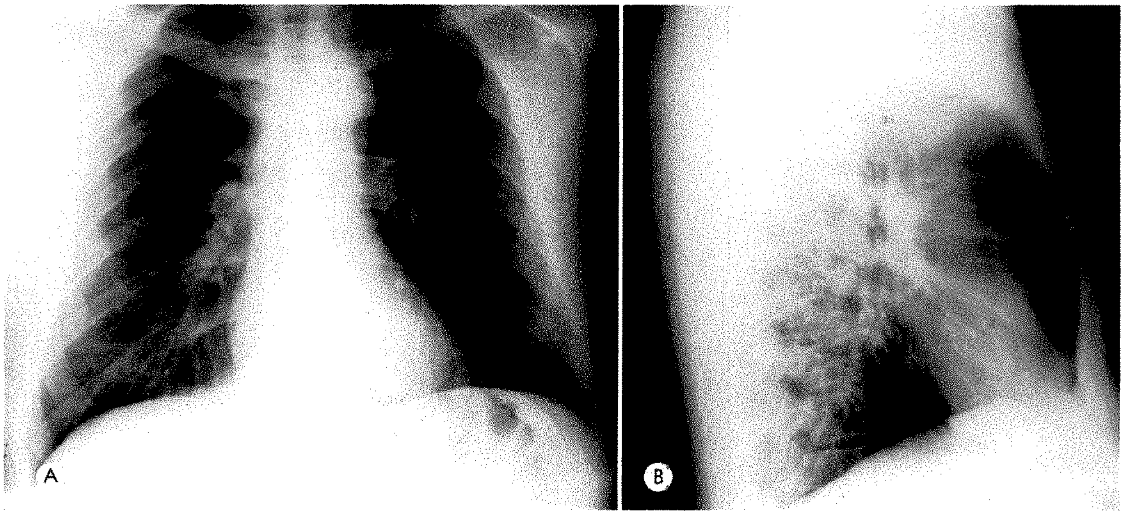

Fig. 3. (*A*) Posteroanterior and (*B*) lateral roentgenograms of the chest made 3 months after Figure 1, *A* and *B*, showing slight residual hilar lymphadenopathy and on *B* a slight increase in the basilar markings.

The case reported here illustrates what appear to be the typical findings in adult measles: dramatic regression of hilar lymphadenopathy and lymphogenous accentuation, with some residual pulmonary infiltration 3 months later. The part the concomitant adenovirus infection had in the clinical and roentgen findings is not known.

SUMMARY

1. A case of adult measles is presented with positive roentgenographic findings in the chest.
2. The chest findings in adults are similar to those in children affected with rubeola.
3. Two different types of giant cells have been described with measles infection: (1) the Warthin-Finkeldey giant cells which involve the lymph nodes of the reticuloendothelial system, and (2) the syncytial epithelial giant cells which are associated with interstitial pneumonitis (giant cell pneumonia) in the lung bases.
4. The extreme hilar lymph node enlargement due to measles reaches a peak in the late prodromal stage and begins to regress when the rash appears.
5. The pulmonary abnormalities in measles usually have occurred by the time of the rash eruption but may reappear and progress to fatal giant cell pneumonia after the rash has disappeared and the reticuloendothelial system has returned to normal.

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BRONCHOGRAPHY IN INFANTS AND CHILDREN

BARIUM SULFATE AS A CONTRAST AGENT

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VARIOUS contrast media have been used for bronchography in children and adults. None is ideal. Objections are directed toward the chemical agent producing contrast (iodine compounds) or toward the suspending agent (various oils, polysaccharides).

Iodides are dangerous in the rare case of iodine sensitivity and various iodides raise the blood level of iodine for variable periods of time, thus interfering with isotope studies. Iodides in oil may result in elevated blood levels for over a year, whereas the effect of water-soluble agents is usually not noticeable after 6 to 8 weeks. Furthermore, oils leave residues which form granulomas. On the other hand, they are usually less irritating than the water-soluble agents.

The water-soluble contrast media usually have a suspending agent such as sodium carboxymethylcellulose to increase viscosity and prevent alveolization. While this substance could also lead to a foreign body reaction if retained in the lungs, this particular problem is probably greater with the oily media. Sulfonamides have been added to oily contrast substances to increase viscosity, but this also presents an unnecessary hazard in the form of sulfonamide sensitivity and formation of methemoglobin.

Those compounds, highly soluble in water, have proved very irritating. The substances such as propyliodone which are used in so-called water soluble media are usually only slightly soluble in water. Such media are visualized roentgenographically for a much longer period if extensive alveolization occurs; therefore, aspiration and postural drainage are important following bronchography.

Barium sulfate is a rather inert chemical substance; many radiologists have seen patients aspirate barium sulfate with little harmful effect. In 1956, Di Rienzo and Pereira-Duarte[4] of Argentina suggested the use of barium as bronchographic contrast agent in adults. This was followed by the work of Nelson *et al.*[18] in the United States in 1959.

Since 1960 we have been using barium sulfate for bronchography in infants and children.[24] This report is based on the first 58 cases in which barium bronchographies were performed.

PREPARATION OF CONTRAST MEDIUM

Ten grams of micronized barium (micropaque)* is mixed with 20 ml. of an autoclaved 2 per cent solution of sodium carboxymethylcellulose (CMC) in saline. An even suspension of barium in the viscous CMC is easily obtained by adding the CMC to the barium and mixing with a tongue depressor. This can be done a few minutes before the procedure.

TECHNIQUE

The technique for performing bronchography in infants and children at the Tulane Pediatric Chest Clinic was thoroughly

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described by Waring and Killelea.[23] This method is a modification of previous techniques reported by Bates *et al.*[1] and by Bovornkitti and Zabriskie.[2]

Postural drainage is carried out on the evening before and on the morning of the procedure. Pre-anesthetic medication consists of secobarbital (seconal), hydroxyzine hydrochloride (vistaril), and 1-hyoscyamine (bellafoline) in doses proportional to weight.

The procedure is performed with the roentgenographic unit adjoining the surgical suite. Bright lighting is maintained in the room to allow continuous inspection of the patient's color and respirations. Throughout the procedure, the patient's cardiac rate is monitored by at least one operator in addition to the anesthesiologist.

Anesthesia is induced with nitrous oxide and fluothane. Although fluothane may lack the very desirable bronchodilator effect of ether, it is nonexplosive and its rapid action assures fast recovery for effective coughing, deep breathing, and postural drainage.

After tracheal intubation with the largest tube easily introduced, an anteroposterior chest roentgenogram is made to determine the exact position of the endotracheal tube with respect to the carina. The previously measured No. 15 polyethylene catheter is inserted so that the catheter projects 3 to 4 mm. below the inferior opening of the endotracheal tube. It is desirable to have the tip of the tube about 2 to 3 cm. above the carina to ensure delivery of the contrast medium into the desired main stem bronchus and possibly to avoid undue alveolization.

The dose of contrast medium for each lung is 1 ml. per year of age, not to exceed 8 ml. For each lung this dose is divided into 3 fractions. Fraction 1 is one-half of the total dose; fractions 2 and 3 are each one-fourth the total dose. Following each fraction, the patient is positioned to encourage filling of the lower lobe bronchi, the middle lobe or lingula, and the upper lobe bronchi. Unless the disease is primarily left-sided, the right bronchial tree is visualized first.

As quickly as possible, right posterior oblique, right lateral, and anteroposterior roentgenograms are taken. The opaque medium is aspirated and the patient is placed in the Trendelenburg position with his right side up. The roentgenograms are inspected to determine whether certain portions of the right bronchography must be repeated, left bronchography begun, or the procedure terminated. About 1 hour is required to obtain bilateral bronchograms from the beginning of anesthesia to the removal of the endotracheal tube.

In the recovery room the Trendelenburg position is maintained until the child is completely awake. A clear airway is maintained. When conscious and able to take clear fluids, the patient is returned to his ward where postural drainage is continued. An erect posteroanterior roentgenogram is made approximately 24 hours after the procedure to demonstrate clearing.

RESULTS

Fifty-eight bronchographies under general anesthesia have been performed in 52 patients. About one-quarter of the bronchographies were made in infants younger than 2 years and about one-half in children of less than 5 years of age. The great majority were bilateral; the risk involved in bilateral bronchographies is that the patient needs to be given general anesthesia twice and, therefore, evaluation of this aspect is necessary.

Barium sulfate has proved to be a very good contrast agent. The bilateral bronchograms of the patient shown in Figure 1, *A–E* demonstrate very clearly the presence of bronchiectasis in the right middle and lower lobes as well as in the left lower lobe, with relatively little alveolization. The final roentgenogram (Fig. 2), taken 24 hours later, reveals very little residual contrast medium in the lungs. Our experience has shown that a small amount of the contrast agent may remain for several months if there is extensive alveolization. The barium is ultimately removed by one or more

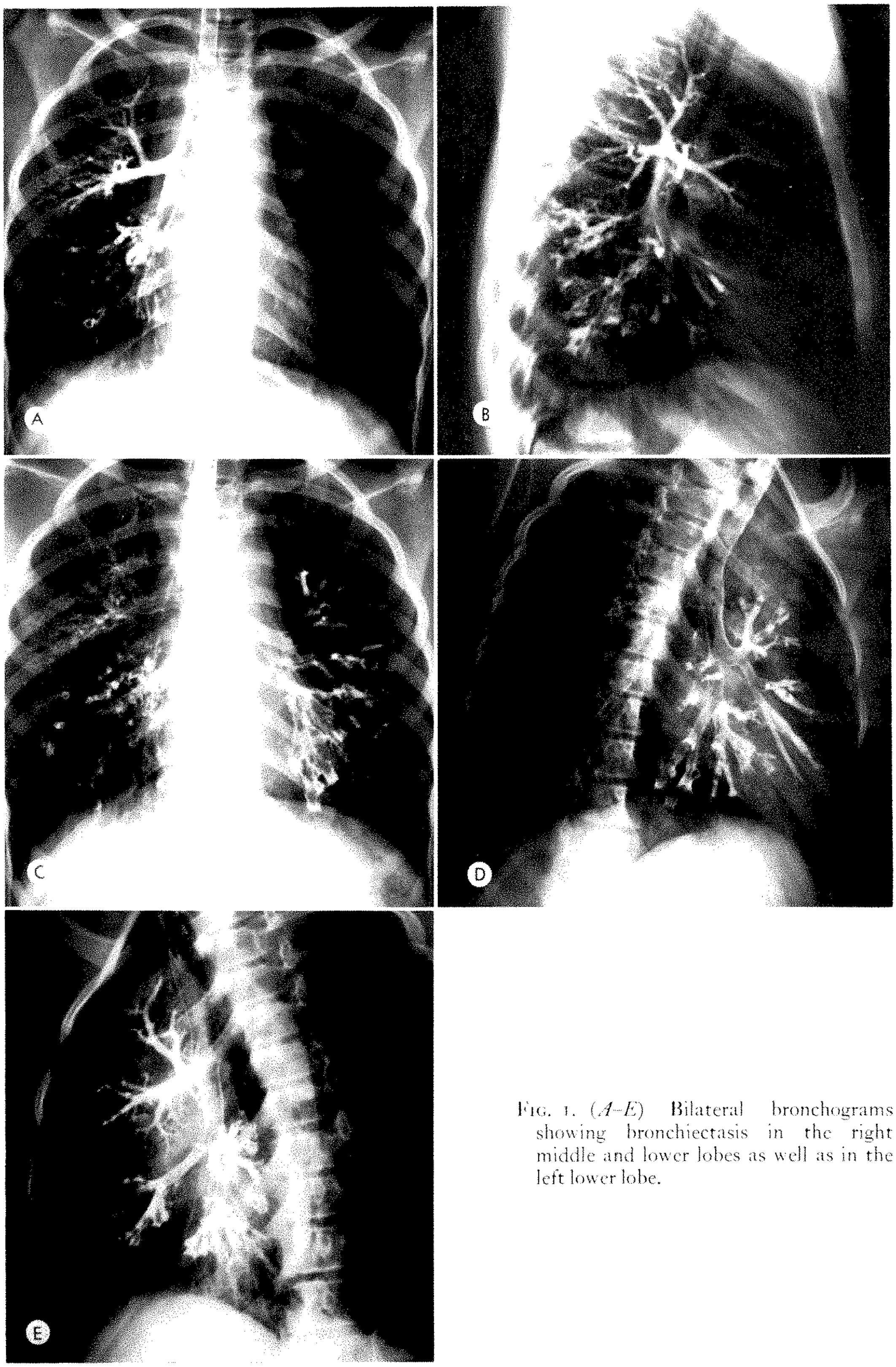

Fig. 1. (*A–E*) Bilateral bronchograms showing bronchiectasis in the right middle and lower lobes as well as in the left lower lobe.

Table I

PERCENTAGE OF SEGMENTS VISUALIZED

	Right (per cent)	Left (per cent)
Complete filling	46.1	37.8
Adequate	41.2	49.7
Unsatisfactory	12.7	12.5

alveolar cleansing mechanisms. We recently saw an adult patient who had residual contrast medium in both lungs from bronchography performed with iodized oil in 1948.

In approximately 86 per cent of our patients, bronchial filling and roentgenographic technique were adequate for diagnosis. The bronchograms were analyzed by segments to show the degree of filling of the bronchi and alveolization. The segments were completely filled or were adequately visualized on 87.5 per cent of the bronchograms (Table I). Approximately 93 per cent of the segments showed zero to slight alveolization, 6 per cent showed moderate and 1 per cent showed pronounced alveolization (Table II). Of 38 patients who had a roentgenogram made 24 hours after the procedure, approximately 78 per cent showed slight or no residue, whereas approximately 22 per cent had moderate residue (Table III). Several others who were followed up to 5 days showed relatively little or sometimes moderate residue.

COMPLICATIONS

Patients usually showed very little temperature change following bronchography. The results of 45 cases were carefully analyzed in this regard. Those with less than an 0.8°F. change were considered of no significance. In 20 cases there was no change, in 19 there was a greater than 0.8° F. decrease in temperature and in only 6 cases, or 13 per cent, was there a greater than 0.8°F. increase in temperature. This usually resolved within 24 hours. Most immediate reactions in bronchography are related to overdosage of anesthetic agents and to varying degrees of ventilatory obstruction caused by viscous material in already diseased lung. In this series, there was 1 instance of cardiac arrest, 1 of bradycardia and 3 of asymptomatic lobar collapse.

Table II

PERCENTAGE OF SEGMENTS SHOWING ALVEOLIZATION

	Right (per cent)	Left (per cent)
Zero to slight	93.0	92.7
Moderate	5.5	6.6
Marked	1.5	0.7

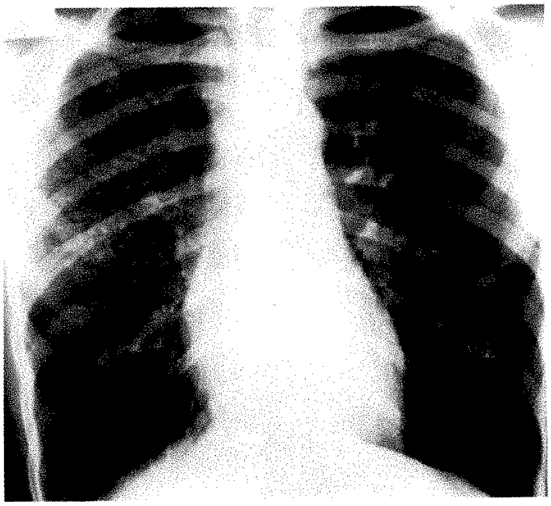

Fig. 2. Roentgenogram 24 hours later showing clearing of the contrast agent.

The cardiac arrest occurred in a 6 year old Negro mongoloid female with achalasia and chronic bilateral pulmonary disease thought to be due to repeated aspiration of esophageal contents. The right lung had been visualized uneventfully and the third fraction of the left bronchography was being carried out when cardiac arrest was noted. As the anesthesiologist cleared the

Table III

BRONCHIAL RESIDUE IN 38 PATIENTS ON 24 HOUR ROENTGENOGRAM

No residue	36.7%
Slight	41.1%
Moderate	22.2%

trachea and endotracheal tube of contrast medium, the chest was opened surgically. The heart was then seen to be beating normally, and the thorax was closed with a catheter drain. She recovered with no further trouble. It is quite possible that this transitory arrest was due to obstruction of the endotracheal tube by the opaque medium.

Cardiac slowing occurred at the same stage of left bronchography in a 2½ year old Negro girl with recurrent pneumonia and possible mitral insufficiency. The bradycardia disappeared immediately with removal of the opaque medium from the tube and trachea.

Of the 3 children with asymptomatic lobar collapse, 1 had partial bronchial construction produced by a foreign body and the remaining 2 had tuberculosis. The addition of the viscous contrast material apparently completed the obstruction. Usually, this obstruction is brief because the opaque medium is progressively diluted by secretions and moved toward the trachea by ciliary and gravitational forces. However, each of these children were inspiring a gas mixture with high partial pressure of oxygen. Rahn[20] has shown that a gas such as nitrogen which diffuses more slowly retards the rate of collapse of the lobe following occlusion of its bronchus. Perhaps in these patients a gas mixture should have been used with a slightly lower percentage of oxygen so that nitrogen would not be completely eliminated from the alveoli.

Pathologic studies were carried out on 8 patients in whom pulmonary tissue had been removed. These specimens were reviewed by Dr. Herbert Ichinose, of the Department of Pathology at Tulane. He stated that in his opinion there were no true pathologic changes which might be ascribed to the contrast substance. The barium sulfate, and to a lesser extent, the sodium carboxymethylcellulose particles, are phagocytized similarly to a rather innocuous foreign body. No evidence of an acute inflammation in response to either was noted. Apparently, the phagocytized particles are removed by the lymphatics. Small aggregates of macrophages were noted in the periphery of peribronchial lymphoid nodules and in the areolar tissue of the lobular septa and internal areolar layer of the pleura.

DISCUSSION

Roentgen contrast studies of the various parts of the tracheobronchial tree are often of critical diagnostic value in patients of any age group. The symptoms indicating need for these studies are chiefly cough, stridor, wheezing, or roentgenographic signs resulting from bronchial or tracheal obstruction and other changes of a chronic nature.[8-16] The immediate complications associated with bronchography include those associated with an overdose of anesthesia, iodine sensitivity, and obstruction of already diseased bronchi. Late complications include retention of the contrast agent with formation of granulomas or interference with interpretations of serial roentgenograms or isotope studies.

Rivero[21] has performed bronchography in children up to 2 or 3 years of age with preliminary sedation and no general or local anesthesia. Theodos[22] has reported desensitization with corticotropine to carry out bronchography with iodized oil in a patient who was sensitive to a skin test with the contrast substance and to an oral dose of 5 mm. of potassium iodide oil. Flooding the entire bronchial tree with a viscous contrast agent leads to anoxia, and, if an agent with too great a degree of viscosity is used, sometimes a cast-like mold may develop in the tracheobronchial tree which is very difficult to expel. The formation of granulomas in the lung has been reported in the past with the use of almost any contrast agent which had been retained for considerable periods of time.

Many other agents have been used in bronchography; a very thorough investigation of this subject was made by Dunbar *et al.*[6] Two of the most popular contrast agents during the past few years have been the oily and aqueous forms of dionosil.[11,19]

A good bronchographic contrast medium should be nonirritating, should be viscous enough to allow filling of the bronchial tree without excessive alveolization, should remain in the bronchial tree long enough to allow satisfactory diagnostic roentgenograms and should be cleared rapidly from the lungs. Holden[10] has described the behavior of contrast media in the bronchial tree very clearly. There seems to be little doubt that contrast medium in the trachea and in large and medium size bronchi can be more quickly recovered when postural drainage is employed, and this effect can be enhanced by coughing. In the smaller bronchi and bronchioles, clearing is the result of ciliary and smooth muscle activity, with the rate of clearance being greatly increased when aided by gravity. In bronchioles of less than 0.4 mm. in diameter, ciliated epithelium is beginning to disappear and goblet cells are absent; therefore, absorption is more likely to occur in these areas. It is in these regions also that the more highly soluble and therefore more irritating contrast substances are apt to cause inflammatory changes. Contrast agents with low solubility tend to be retained in these regions and thereby increase the chance of granulomatous formations.

In the past, many investigators assumed that barium could not be cleared from the tracheobronchial tree because of its low solubility in aqueous solutions. Willson *et al.*[25] reported on 16 patients who accidentally aspirated barium. It was found that the barium was not retained and there was no immediate or delayed reaction. Dunbar *et al.*[6] studied various contrast agents because of their interest in the swallowing mechanism in infants who tended to choke during feeding. They injected contrast agents in the tracheobronchial tree of rats, using barium and tap water, barium in 10 per cent sucrose solution, aqueous dionosil, lipiodol, and tap water. They concluded that there was no great difference in the reaction produced by these agents. On the other hand, retention of barium for a considerable period of time, resulting in formation of granulomas in the lungs[7] and in the abdomen,[14,15] both in humans and in experimental animals, has been reported. Relatively mild reactions have been obtained after injecting barium into the tracheobronchial tree of rats[12] and dogs,[25] although it has been noted that if the barium is injected below the carina there is likely to be flooding of the alveoli and more retention of the contrast substance. Johnson *et al.*[13] found that, of 8 contrast agents injected into the tracheobronchial tree of rabbits, a mixture of barium sulfate plus carboxymethylcellulose caused the worse reactions. The absence of smooth muscle in the bronchioles of rabbits[9] may account for the poor results.

Nelson and his co-workers[17,18] have indicated that barium sulfate (micropaque) suspended in normal saline which contains at least 1.5 per cent sodium carboxymethylcellulose is a safe bronchographic contrast material. They obtained a significantly smaller incidence of minor nonspecific reactions (elevated temperature, increased pulse rate, etc.). They also emphasized the usefulness of this type of agent if there is any question concerning iodine sensitivity. One unique feature which they noted is that barium particles apparently adhere to the wall of an infected cavity for a long period of time and can be seen on chest roentgenograms. They have not seen this following the use of other contrast agents. In their opinion, barium should not be used in cases of emphysema because it is retained longer.

Cember *et al.*[3] employed a method of intratracheal insufflation of barium sulfate particles directly through the pharynx for the investigation of particulate matter in the lungs. These particles were easily expelled from the deep part of the respiratory tract in rats and presumably the same would happen in humans. In our laboratory, experiments are being conducted to determine whether insufflated barium sulfate particles may prove useful in outlining the tracheobronchial tree.

SUMMARY AND CONCLUSIONS

Barium sulfate has been used as a contrast agent in 58 bronchographies performed in infants and children. This contrast agent is considered safe for bronchography; few reactions were associated with its use and very few pathologic sequelae were noted in removed surgical specimens. The reactions that were encountered were most likely the result of anoxia or acute obstruction of the tracheobronchial tree. These hazards may be circumvented by adequate postural drainage before and after the procedure, anesthesia of moderate depth, and avoidance of inhalation of very high concentrations of oxygen.

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ACUTE RESPIRATORY DISTRESS IN AN INFANT PRODUCED BY HYPERTROPHIED TONSILS*

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ACUTE respiratory distress in infants due to tonsillar enlargement is rare. A review of the literature of the past 13 years revealed but 2 cases of acute tonsillitis and acute adenoiditis in children under 2½ years of age who required emergency tracheostomy.[2] To our knowledge acute respiratory distress due to uninflamed hypertrophied tonsils has not been recorded.

REPORT OF A CASE

I.S., a 9 month old infant patient of Dr. A. Kantrow, was admitted to the hospital because of recurrent respiratory distress of unknown

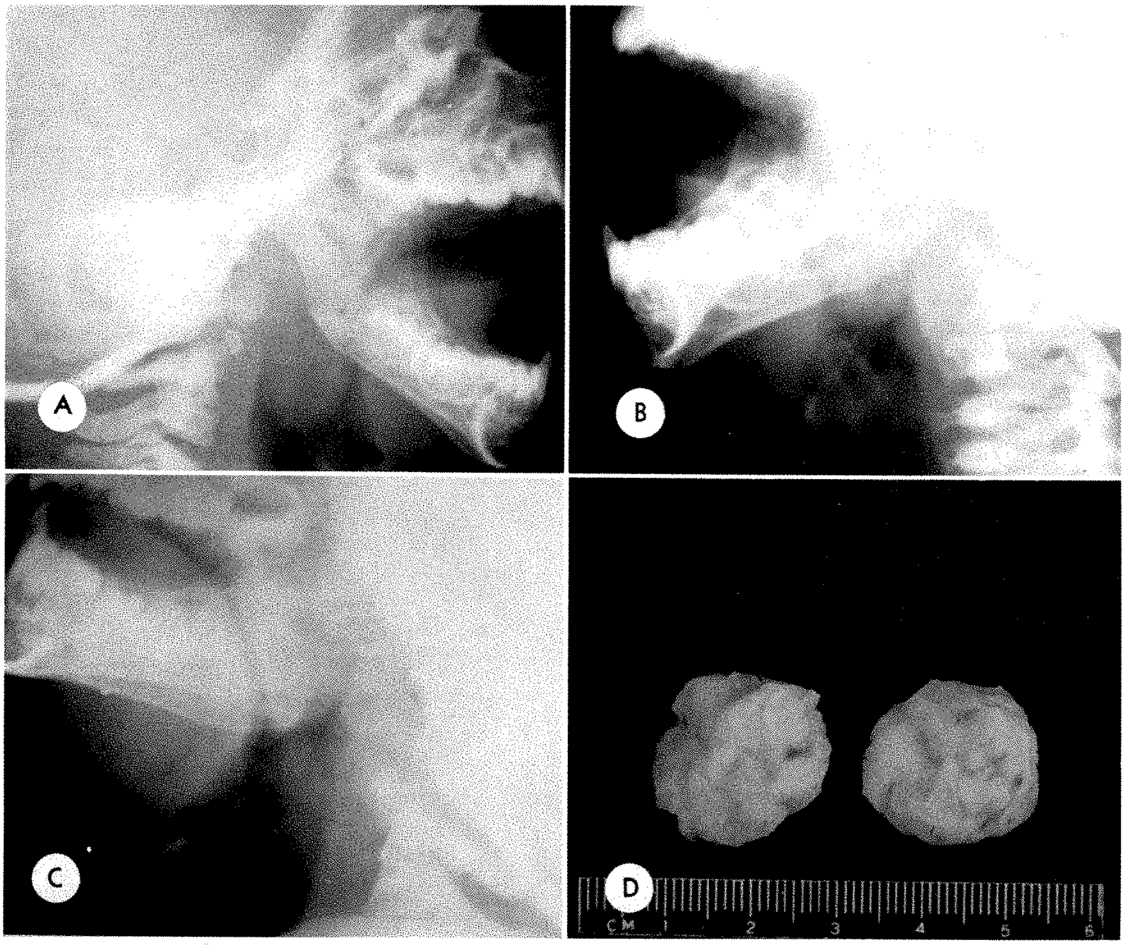

Fig. 1. (*A*) Lateral roentgenogram made while the patient was crying. The soft tissue mass has moved down and appears to be obturating the oral pharynx. (*B*) Lateral roentgenogram of the nasopharynx at rest. A rounded soft tissue density is seen projecting towards the larynx. (*C*) The nasopharynx after tonsillectomy. The air passages are normal. (*D*) The specimens of the tonsils measure about 3 cm. in diameter.

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origin. The child's mother noted that he would suddenly hold his breath while crying and become cyanotic. At times breathing would be resumed only after the child was shaken vigorously.

Physical examination disclosed diffusely enlarged tonsils. No inflammatory changes were present in the nasopharynx. Scattered rales were heard over both sides of the chest.

Roentgenographic examination of the chest was normal except for moderate thymic enlargement which was considered to be within normal limits and of no clinical importance. The blood cell count and other laboratory data were within average limits.

On the third day of hospitalization, it was observed that the child became cyanotic while being positioned for an upright chest roentgenogram and that normal breathing and color returned when the child was placed in a prone position. Lateral roentgenograms of the nasopharynx were then obtained while crying and during rest (Fig. 1, *A* and *B*). At rest a soft tissue density was observed. This presented towards the larynx as a rounded mass and an adequate airway was seen. The roentgenogram obtained while the patient was crying revealed a downward displacement of the mass towards the pharynx which diminished the airway perceptibly. The adenoids also were hypertrophied. Consultation was immediately obtained and the laryngologist (E.S.) concurred that the soft tissue mass was consistent with the presence of an enormously enlarged pair of tonsils which did not appear to be inflamed. The lower margin of the tonsils could not be seen. It was possible to produce the symptom complex of cyanosis and cessation of respiration by holding the patient erect or in the supine position and to relieve it by placing the patient in a prone position. Tonsillectomy was performed about 6 hours later (Fig. 1*C*). Adenoidectomy was not performed at this time. The tonsils were not acutely diseased, and each measured 3 cm. in diameter (Fig. 1*D*). The patient made an uneventful recovery.

COMMENT

Tonsillar swelling does not usually produce serious respiratory obstruction even though the airway may appear obstructed. The more common causes of respiratory obstruction in infants include infections such as peritonsillar or retropharyngeal abscesses, epiglottitis, congenital malformations such as laryngeal webs and cysts. Extrinsic pressure from enlarged thymus glands no longer is considered an adequate explanation, as was noted in the present instance. Occasionally, a tumor such as a cystic hygroma may be associated with respiratory distress. Other reasons include congenital malformations of the heart, pulmonary infections or mediastinal tumors. As a rule these can be identified by adequate examination. Viral and bacterial infections of the air passages also can be diagnosed clinically. Aspiration of foreign bodies is another possible cause of respiratory distress. All of these had been under consideration. However, the presence of tonsils sufficiently enlarged to cause mechanical obstruction of the oral pharynx was not suspected until the roentgeographic examination of the neck disclosed the soft tissue masses projecting into the air passage.

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VARIATIONS IN THE DEPTH OF THE CERVICAL PREVERTEBRAL TISSUES IN NORMAL INFANTS STUDIED BY CINEFLUOROGRAPHY*

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ABSCESS in prevertebral tissues of the neck is mainly a disease of children in the first 3 years of life. During this age the prevertebral tissues contain a variable number of lymph nodes.[4] Infection, which usually originates in the nasopharyngeal area or middle ear,[5] spreads by way of the lymph channels to the prevertebral lymph nodes. The lymphadenitis could then lead to a prevertebral abscess. If the abscess is not treated, it may dissect into the posterior mediastinum and cause respiratory embarrassment or necrosis and rupture of the great vessels of the neck. Spontaneous rupture into the pharynx with aspiration and lung abscesses is another serious complication.[4] Early recognition and treatment of this disease are, therefore, important.

The incidence of retropharyngeal abscess in infants has decreased sharply since the advent of antibiotics; however, its occasional development and serious prognosis still make its accurate diagnosis important.

The role of roentgenology in the diagnosis of cervical prevertebral abscess is well known. Most authors mention that lateral roentgenograms of the pharynx may be helpful.[1–3,7–9] Thickening of the prevertebral tissues with anterior displacement of the pharyngeal air shadow is the diagnostic roentgenographic finding. Pendergrass, Schaeffer and Hodes[10] recognized that in

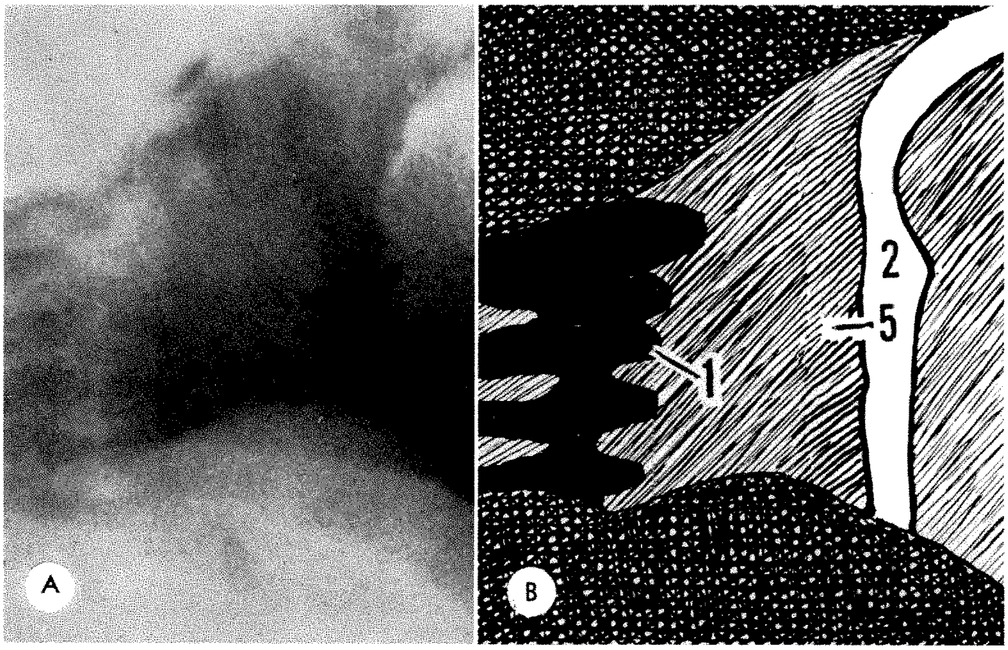

FIG. 1. (*A*) Cineroentgenogram showing that at the depth of expiration the prevertebral tissues are thick, simulating a retropharyngeal abscess. (*B*) Line tracing showing (1) cervical spine, (2) pharynx, and (5) retropharyngeal space.

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infants, the prevertebral tissues thicken during expiration and become thin during inspiration. They emphasized that the roentgenogram must be made at the peak of inspiration to assure a minimal depth of prevertebral tissues.[10] If the roentgenogram happens to be made during expiration, the prevertebral tissues thicken and a retropharyngeal abscess is simulated (Fig. 1, *A* and *B*).

Hay[6] states that during the first year of life the normal thickness of the prevertebral tissues never exceeds 1.5 times the anteroposterior depth of the body of the fourth cervical vertebra, and from 1 to 2 years of age it does not exceed 0.5 times the anteroposterior depth of the body of this vertebra.

The difficulty of making a roentgenogram at the peak of inspiration in an infant is well known and was verified in our work. Cinefluorograms obviate this difficulty and demonstrate the thickness of the prevertebral tissues accurately during all phases of the respiratory cycle.

MATERIAL AND METHODS

Infants under 2 years of age were studied. Although the patients were affected with many different diseases, they were all normal with respect to the pharynx. Lateral roentgenograms were made of the neck, and an attempt was made to obtain one roentgenogram at the peak of inspiration and one at the depth of expiration. The same subjects were then studied with cineroentgenography. Cineroentgenograms were made in the lateral projection with a 16 mm. camera from the output phosphor of an 8 inch electron image amplifier. The technical factors were 2.5 ma., 65 kv. and 30 frames per second. Usually a short exposure time was sufficient, so that the radiation dose to the thyroid gland was less than 0.2 r. The gonadal dose was negligible. An attempt was made to obtain cineroentgenographic strips during quiet breathing, crying and swallowing of barium. Since all of the subjects had to be secured to a restraining board, they were usually crying.

RESULTS

Very few of the lateral roentgenograms could be obtained at the height of inspiration. In fact, some of the expiration roentgenograms revealed less thickness of the prevertebral soft tissues than the inspiration roentgenograms. It soon became evident that this method was unreliable.

On cineroentgenograms, the minimal thickness of the prevertebral soft tissues during the inspiration was regularly less

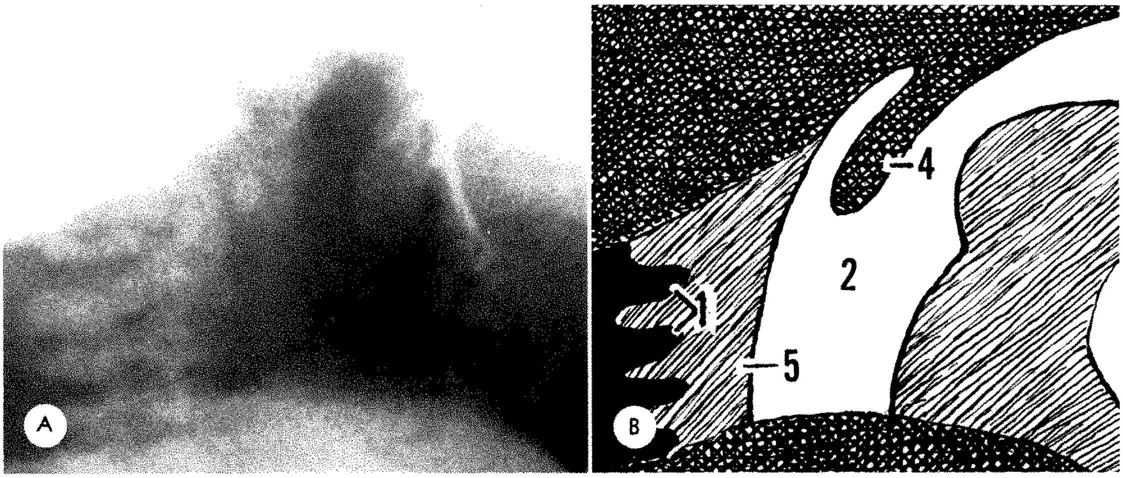

Fig. 2. (*A*) Cineroentgenogram showing that at the peak of inspiration the thickness of the prevertebral tissues is less than the anteroposterior depth of the adjacent cervical vertebra. (*B*) Line tracing showing (1) cervical spine, (2) pharynx, (4) uvula and, (5) retropharyngeal space.

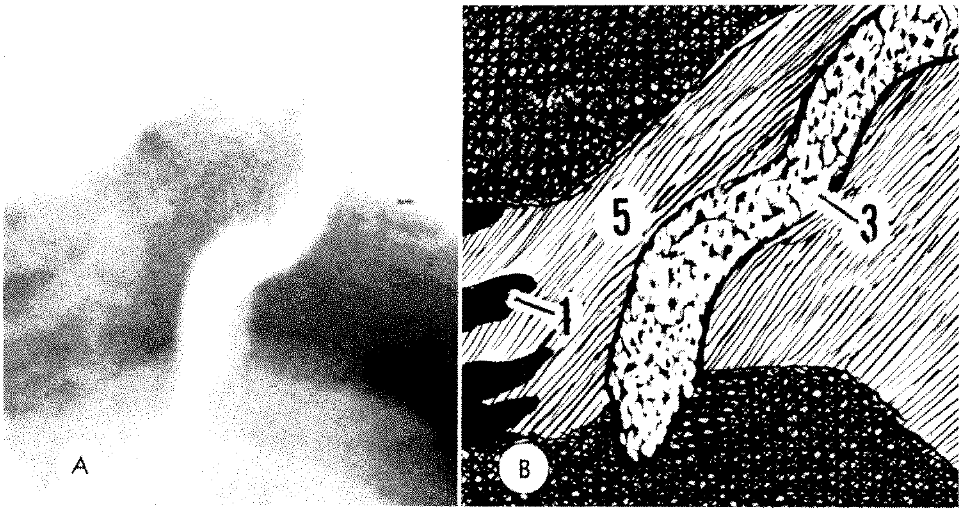

Fig. 3. (*A*) Barium swallow study shows a flattening of the posterior pharyngeal wall out against the anterior surface of the adjacent cervical vertebrae. (*B*) Line tracing showing (1) cervical spine, (3) barium-filled pharynx, and (5) retropharyngeal space.

than the anteroposterior depth of the body of the adjacent cervical vertebra (Fig. 2, *A* and *B*). The duration of minimal thickness lasted only 0.2 second in most cases. In some cases the maximal thickness of the prevertebral soft tissues during expiration approached 3 times the anteroposterior depth of the body of the adjacent cervical vertebra (Fig. 1, *A* and *B*).

Thin prevertebral soft tissues were also demonstrated when the infant swallowed barium. The barium was propelled into the pharynx by the tongue and the posterior pharyngeal wall was flattened out against the cervical spine (Fig. 3, *A* and *B*). Barium studies provided additional information, but are not necessary because the water density of the prevertebral tissues is

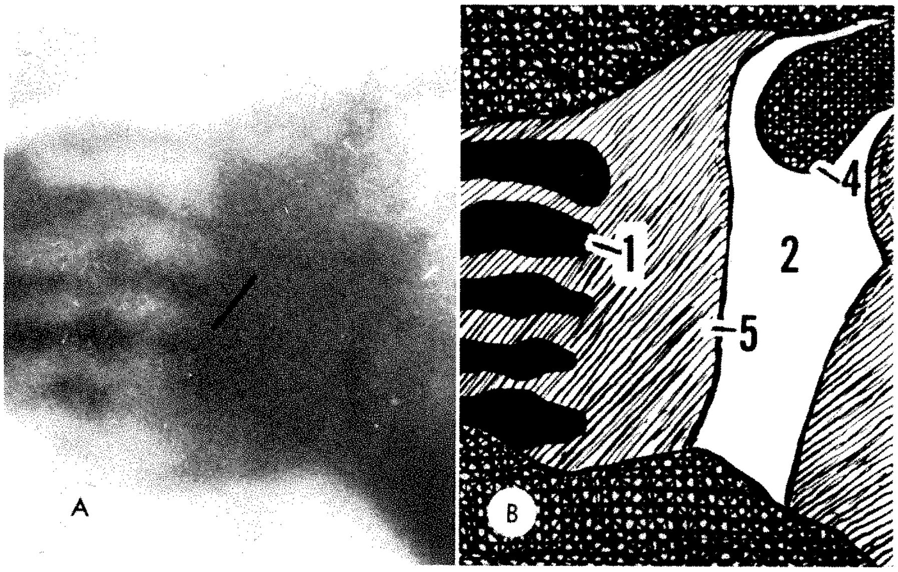

Fig. 4. (*A*) Cineroentgenogram showing that during phonation the soft palate shortens and swells in its transverse diameter. (*B*) Line tracing showing (1) cervical spine, (2) pharynx, (4) uvula, and (5) retropharyngeal space.

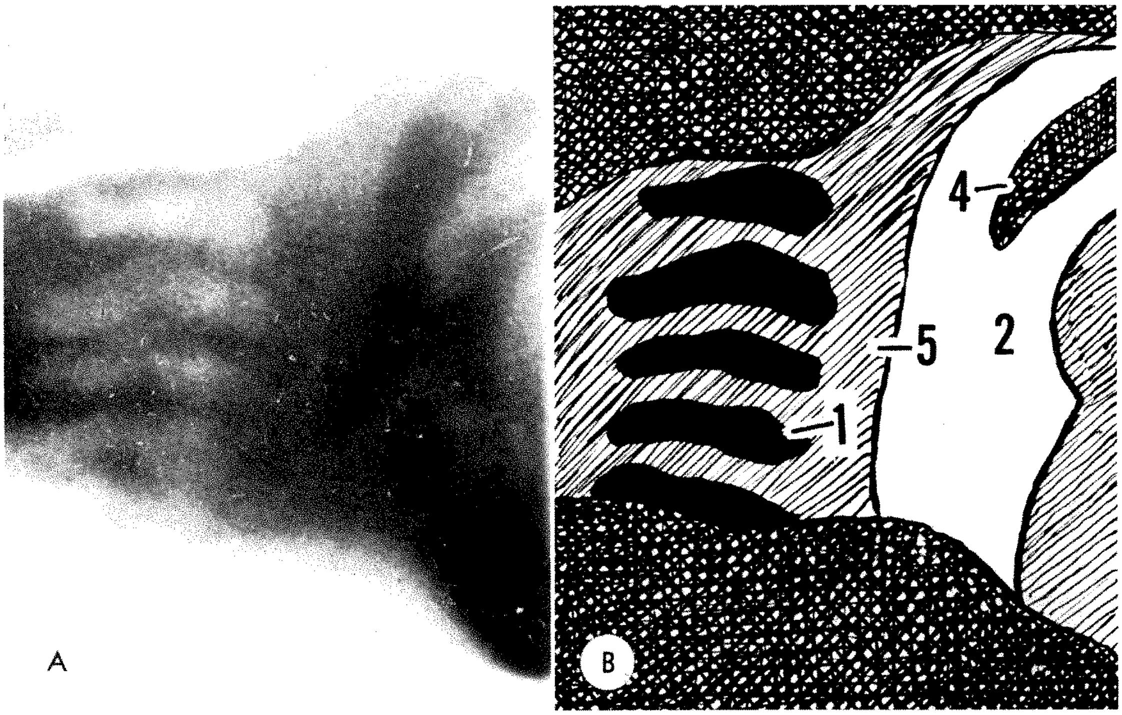

FIG. 5. (*A*) Cineroentgenogram showing that during inspiration the soft palate assumes its long, slender form. (*B*) Line tracing showing (1) cervical spine, (2) pharynx, (4) uvula, and (5) retropharyngeal space.

clearly seen between the contrast of the air column in the pharynx and the bone density of the cervical spine.

When an air-fluid level in the thickened prevertebral soft tissues is seen, a diagnosis of abscess can be made. Cellulitis and lymphadenitis without suppuration also produce swelling of the prevertebral tissues. Despite this, the roentgenographic information is very helpful to the clinician as it prevents the fictitious diagnosis of prevertebral abscess when normal maximal thickness of the tissues is visualized during expiration.

Another interesting phenomenon was demonstrated. During phonation the soft palate rose, shortened and swelled transversely to close the nasopharynx (Fig. 4, *A* and *B*). When phonation ceased, the soft palate again assumed its long, slender form which persisted most of the time (Fig. 5, *A* and *B*). Caution should therefore be used before diagnosing edema of the soft palate from a single lateral roentgenogram.

CONCLUSION

In normal infants cineroentgenograms demonstrated that the cervical prevertebral tissues fluctuate widely in depth during the respiratory cycle. The tissues are thin at the peak of inspiration and thicken during expiration. Often during expiration in normal infants the thickness of the prevertebral soft tissues becomes greater than the thickness used as a diagnostic sign of retropharyngeal abscess.

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SPONDYLARTHRITIS IN CHILDHOOD*

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SPONDYLARTHRITIS is a spinal disorder which appears to be inflammatory in nature. It is characterized by fairly typical clinical and roentgenologic findings and runs a rather rapid course, usually leading to complete and permanent clinical recovery.

One of the first reported cases representing this condition was published by Mayer[15] in 1925. This was a 5 year old girl who developed a kyphosis in the upper lumbar region with narrowing of the intervertebral disk, but, no associated bone destruction. *Staphylococcus viridans* was cultured from the blood.

In recent years an increasing number of articles have appeared dealing with the subject under various names, such as a study of acute infectious lesions of the intervertebral disks,[10] spondylarthritis in children,[17] benign form of acute osteitis of the spine,[2] destructive lesion involving the intervertebral disk,[14] narrowing of the intervertebral disk space,[6] and nonspecific spondylitis.[12]

MATERIAL

Twenty patients comprise the present series, 5 of whom had the diseased area biopsied: 4 by needle aspiration and 1 by open operation. Though the total number of cases reported in the literature is over 100, very few have been biopsied. Doyle[6] in 1960 reported 16 cases, 3 of which had biopsies. Culture of the material obtained revealed no growth. The pathology reported was acute inflammation of the intervertebral disk in 1 case and chronic osteomyelitis in another. In the third no inflammatory material was found. Jamison and co-workers[12] reported one case in which biopsy was performed with negative results. Childe and Tucker[3] in 1961 discussed a series of 10 cases, 2 of which were biopsied. Neither revealed organisms or inflammatory exudate. Milone *et al.*[16] in 1962 cultured *Staphylococcus aureus* from 4 of their 7 patients in whom there was involvement of the spine. In Table I are the findings in the present series. *Staphylococcus aureus* was cultured in 2; in the remaining 3 purulent blood stained material was reported at the time of operation; however, cultures revealed no growth.

CLINICAL FEATURES

The early diagnosis is often difficult, though in established spondylarthritis the clinical and laboratory findings are fairly typical and, when evaluated with roentgenograms, should suggest the correct

TABLE I

BIOPSY RESULTS

Case I	Needle Biopsy	Purulent blood stained material; culture—no growth
Case II	Disk Curettage	Pathology report—granulation of tissue and bone; culture—*Staphylococcus aureus*
Case III	Needle Biopsy	Blood and pus; culture—no growth
Case IV	Needle Biopsy	Purulent material; culture—*Staphylococcus aureus*
Case V	Needle Biopsy	Blood and purulent material; culture—no growth

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diagnosis. The condition is encountered mainly in infants and young children. Of the 20 cases reported, 14 were under the age of 4 years, 4 were from 4 to 8 years, and only 2 were in the 10 to 14 year age group (Fig. 1). The sex incidence showed a slight preponderance of males in a ratio of 12 to 8. Other series have shown the incidence to be equal or with a slight male predominance except for that reported by Doyle[6] in which there was a slight increase in the number of females.

There may be a history of a mild infection or trauma, usually to the back. Following this the child is usually well from several days to 3 to 4 weeks at which time there may be complaints referable to the lower portion of the spine. This may be in the form of pain or may be manifest by stiffness of the back, spasms with crying or a regression from walking to sitting and then to lying with subsequent refusal to sit or stand. Less frequently, the initial complaint is not related to the spine, but to the hip. In these cases there is pain which may be manifest by a limp or by crying in an infant who is having the diaper changed. Abdominal pain as the presenting symptom is sometimes encountered and was noted in 1 case in this series. Meningeal signs, with a positive straight leg raising test, may be present, though in 6 of the present cases in which a lumbar puncture was performed the cerebrospinal fluid was normal. The 4 presenting symptoms of spondylarthritis as pointed out by Guri,[11] Dupont and Andersen[7] and others are: (1) low back pain; (2) hip pain; (3) abdominal pain; and (4) meningeal signs. These need not occur separately and more than one may be found in any one patient. The complaints are often accompanied by a history of irritability, loss of appetite, some fever and easy fatigability.

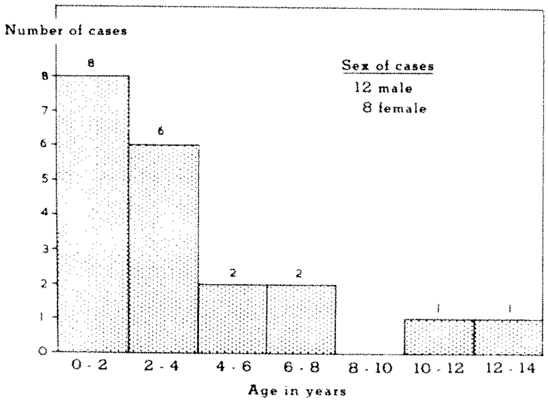

Fig. 1. Age and sex of patients.

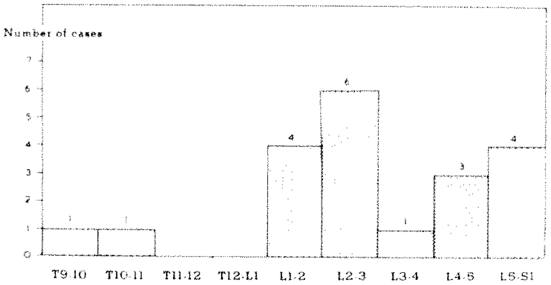

Fig. 2. Level of intervertebral disk involvement.

On physical examination the children are only mildly to moderately ill with a fever ranging from 99°F. to 103°F. The child may refuse to sit or stand preferring to lie supine or on one side with the hips flexed due to irritation of the psoas muscles. The paravertebral muscles are in spasm and there is loss of the normal lumbar lordotic curve. There may be accompanying scoliosis. In 2 patients there was a mild gibbus deformity in the lumbar area accompanying the rigid back. Any attempt to flex or extend the spine or straight leg raising accentuates the pain. Tenderness over the involved portion of the spine is frequently present and was noted in 13 cases.

Leukocytosis does not appear to be a prominent feature and when present is slight. Early in the condition an elevated sedimentation rate is the most consistent laboratory finding. The tuberculin skin test is negative to all strengths. The Widal agglutination test is normal. In 10 patients a blood culture was done with negative results in 9. In the tenth, in whom there was a positive biopsy of the spinal lesion, culture produced pyogenic staphylococcus.

Figure 2 shows graphically the level of involvement in the 20 cases. The lumbar spine is the region of predilection with only a small percentage of cases occurring in the lower thoracic area.

ROENTGEN FINDINGS

The roentgenologic changes lag behind the clinical signs and symptoms. Various authors[2,3,12,17] have stated that the changes are first seen from 2½ to 3 weeks after the onset of symptoms. The time lapse in this series ranged from 2 to 4 weeks. In 3 cases the initial roentgenograms made 1 to 2 weeks after the onset of symptoms were normal, though subsequent roentgenograms at 4 weeks showed disk space narrowing. This is followed in approximately 1 to 2 weeks by under-mineralization of the adjacent vertebral margins, which lose their clear cut outline and appear irregular. This never involves more than one quarter of the contiguous portion of the body and often less. Sometimes a small radiolucent defect is seen in one or both vertebral margins due to localized erosion of the body. A paraspinal mass is not a prominent feature when the lesion is located in the lumbar region and was present in only 1 case (Fig. 3, *A* and *B*). In both cases involving the lower thoracic spine, an accompanying mass was present. On occasions, there is a localized mild scoliosis or kyphosis due presumably to eccentric disk narrowing and muscle spasm. During the next 1 to 3 months, the disk space usually becomes narrower and the vertebral margins gradually become more distinct as remineralization takes place. In some, however, the disk becomes wider rather than narrower due to an extreme degree of under-mineralization of the vertebral margins and in these the vertebral height appears decreased. This process may in turn be followed by narrowing as remineralization occurs. The subsequent course may show persistent narrowing of the disk with vertebral margins which are either smooth or irregular in outline and often may reveal some reactive sclerosis. On the other hand the disk space may return almost to normal width in some instances (Fig. 4, *A–D*). In 2 cases follow-up exami-

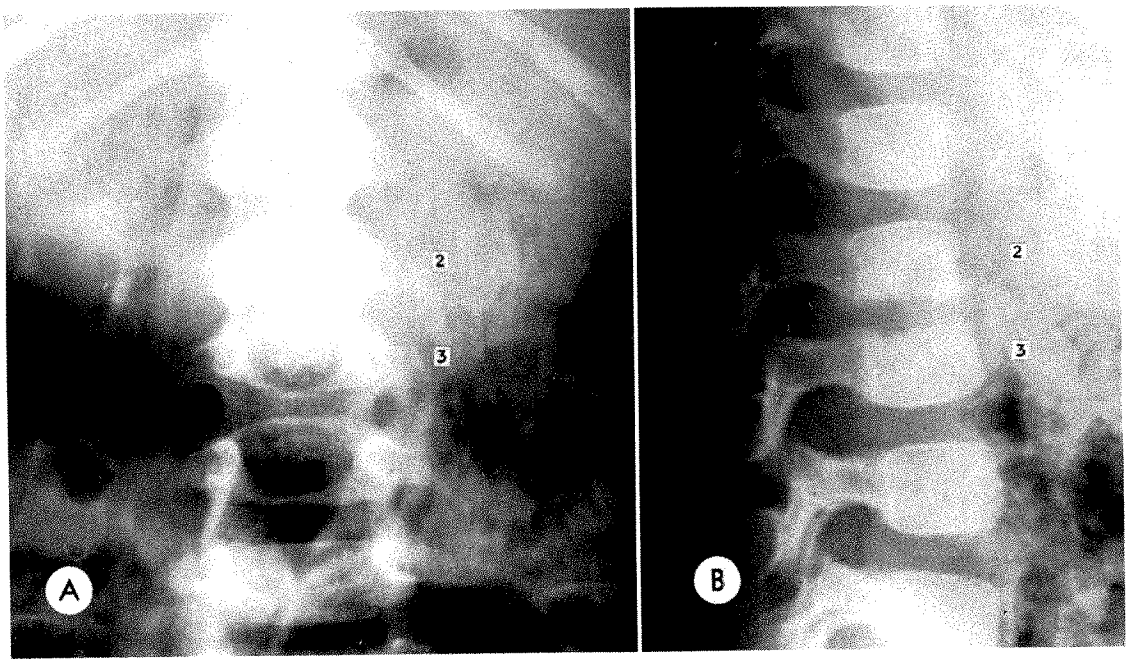

Fig. 3. Case 1. Two year old female, November, 1945. (*A* and *B*) Disk space at L2–3 slightly narrowed with under-mineralization and irregularity of adjacent vertebral margins. Minimal paraspinal swelling at the involved level seen on *A*.

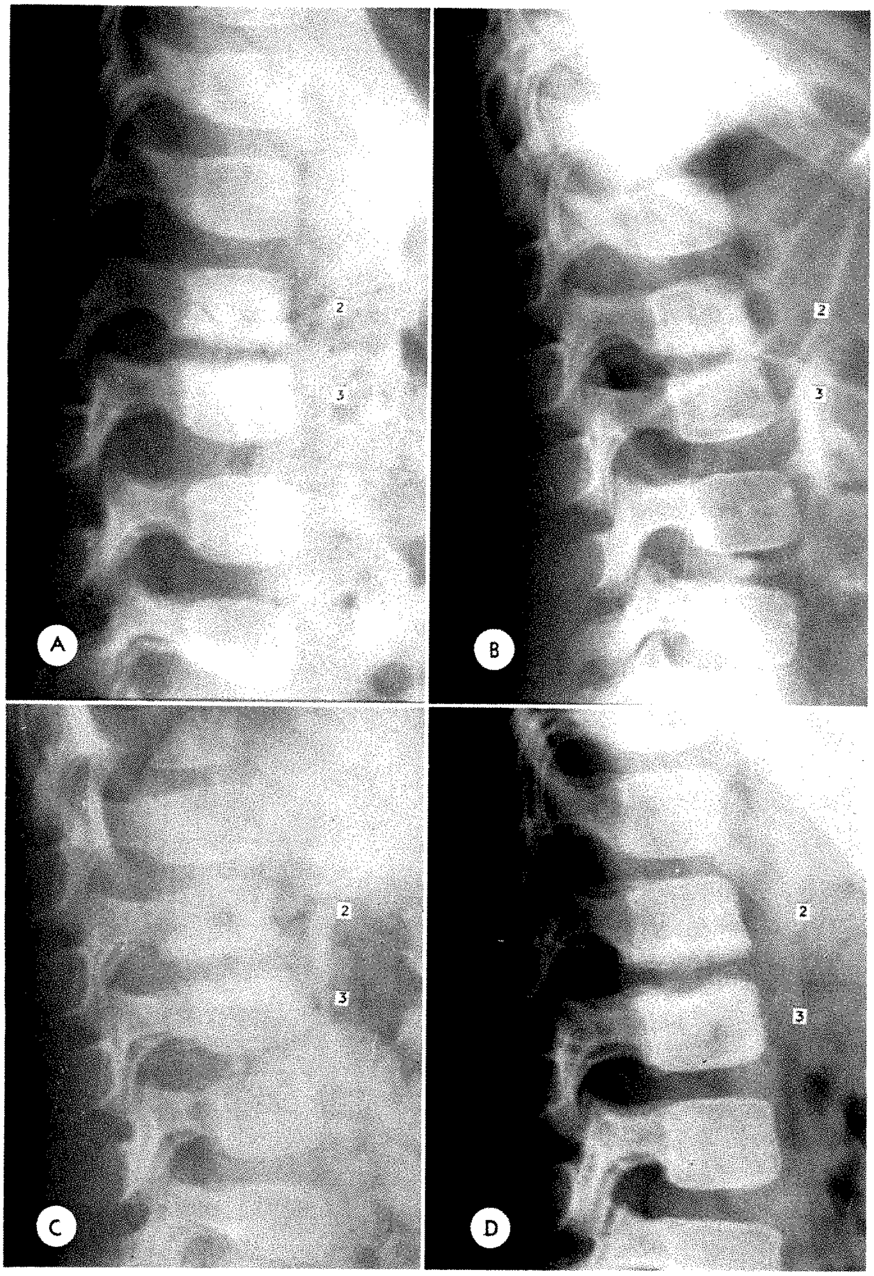

FIG. 4. Case 1. Subsequent course showing further narrowing followed by gradual widening and reactive sclerosis. (*A*) January, 1946; (*B*) February, 1946; (*C*) April, 1946; and (*D*) June, 1947.

nations 6 and 7 months respectively after the commencement of roentgenologic changes showed that the spacing had returned almost to normal. In a third case (Fig. 5–8, inclusive) it returned to near normal in 10 months, then, following recurrence of backache, became narrower over the next 3 years and showed no change on follow-up examinations over 2 years and 4 months. The increase in the disk spacing occurring in the later months is probably due to fibrous tissue formation. Follow-up examinations extending over periods from $2\frac{1}{2}$ months to 6 years, 2 months have shown only minimal bony fusion in 1 case, and in this a biopsy by curettage had been performed.

PATHOGENESIS

Prior to the onset of symptoms, there is frequently a history of trauma to the back or infection. Seven cases in this series revealed evidence of infection alone; in 6 there was combined infection and trauma, while in only 1 was there a history of trauma alone. In 4 instances there was no history of either and in 2 the clinical information was incomplete. The sites of possible infection are the upper respiratory tract, the skin and the teeth, though these may not be readily apparent and a careful history and physical examination must be carried out. The urinary tract is also mentioned in the literature as a possible site, but there was no evidence to suggest infection from this source in this series.

If trauma and infection are considered as possible precipitating factors and the disorder is regarded as representing an inflammatory process which starts either in the intervertebral disk or the vertebral body, the nature of the blood supply to these regions is important. Smith[18] in 1931 examined the intervertebral disk at autopsy in 57 cases and found that nutritive canals do exist. These are derived from the marrow of the vertebral body and reach the nucleus pulposus by first piercing the cartilaginous plate of the disk, then running between the fibers of the annulus fibrosus. Smith regarded these as blood vessels. Further reports by Coventry *et al.*[4] in 1945 on the microscopic anatomy of the intervertebral disk in 88 cases ranging from 10 months to 79 years of age and by Ferguson[9] in 1950 in 24 fetuses and infants confirmed the presence of vascular channels entering the disk from the spongiosa of the vertebral body. Coventry and co-workers[4] noted that these channels had largely disappeared by the age of 10 years, but some were found to persist up to the third decade. These observations support the earlier work of Umbermuth in 1929 and Bohmig in 1930. The latter found the blood supply to be present until the age of 20 years.

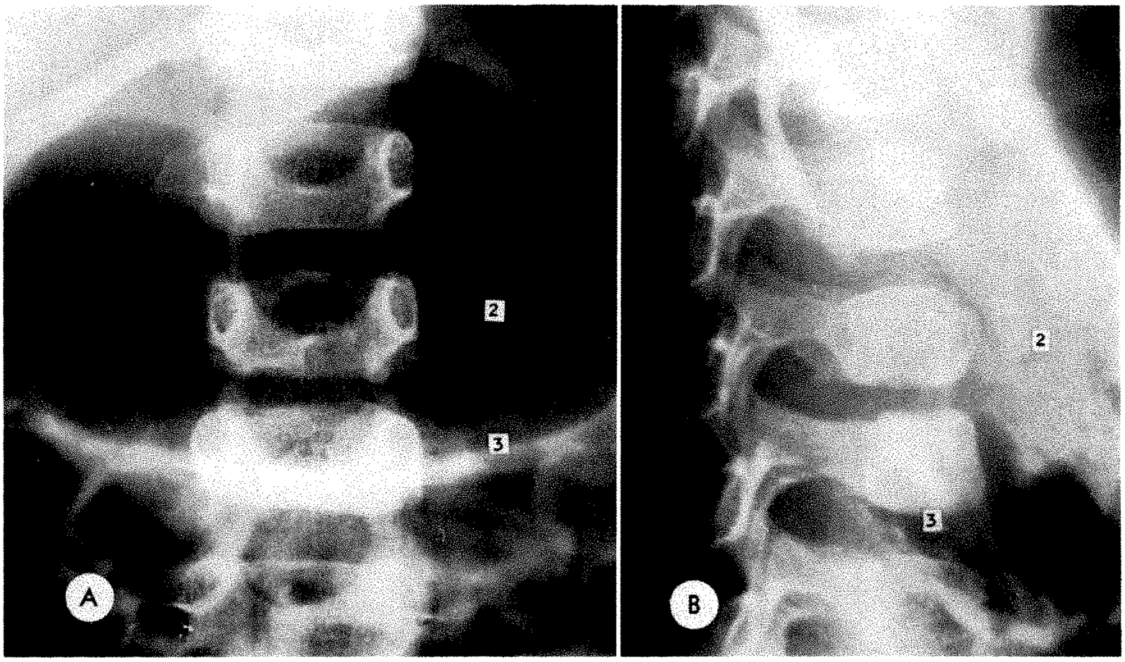

Fig. 5. Case 11. Two year old female, November, 1955. (*A* and *B*) Mild disk space narrowing at L2–3. Minimal under-mineralization of adjacent vertebral margins.

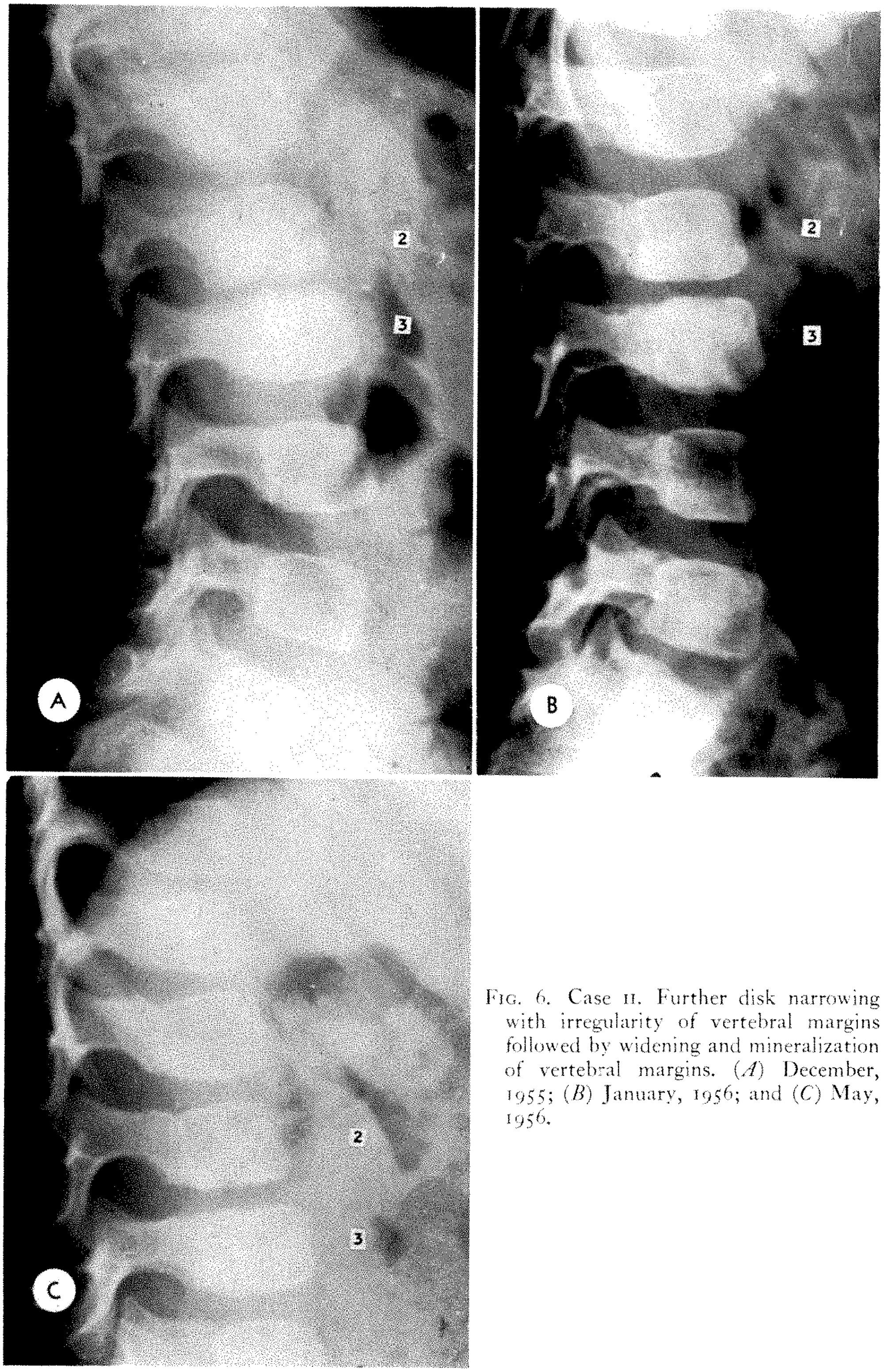

Fig. 6. Case II. Further disk narrowing with irregularity of vertebral margins followed by widening and mineralization of vertebral margins. (*A*) December, 1955; (*B*) January, 1956; and (*C*) May, 1956.

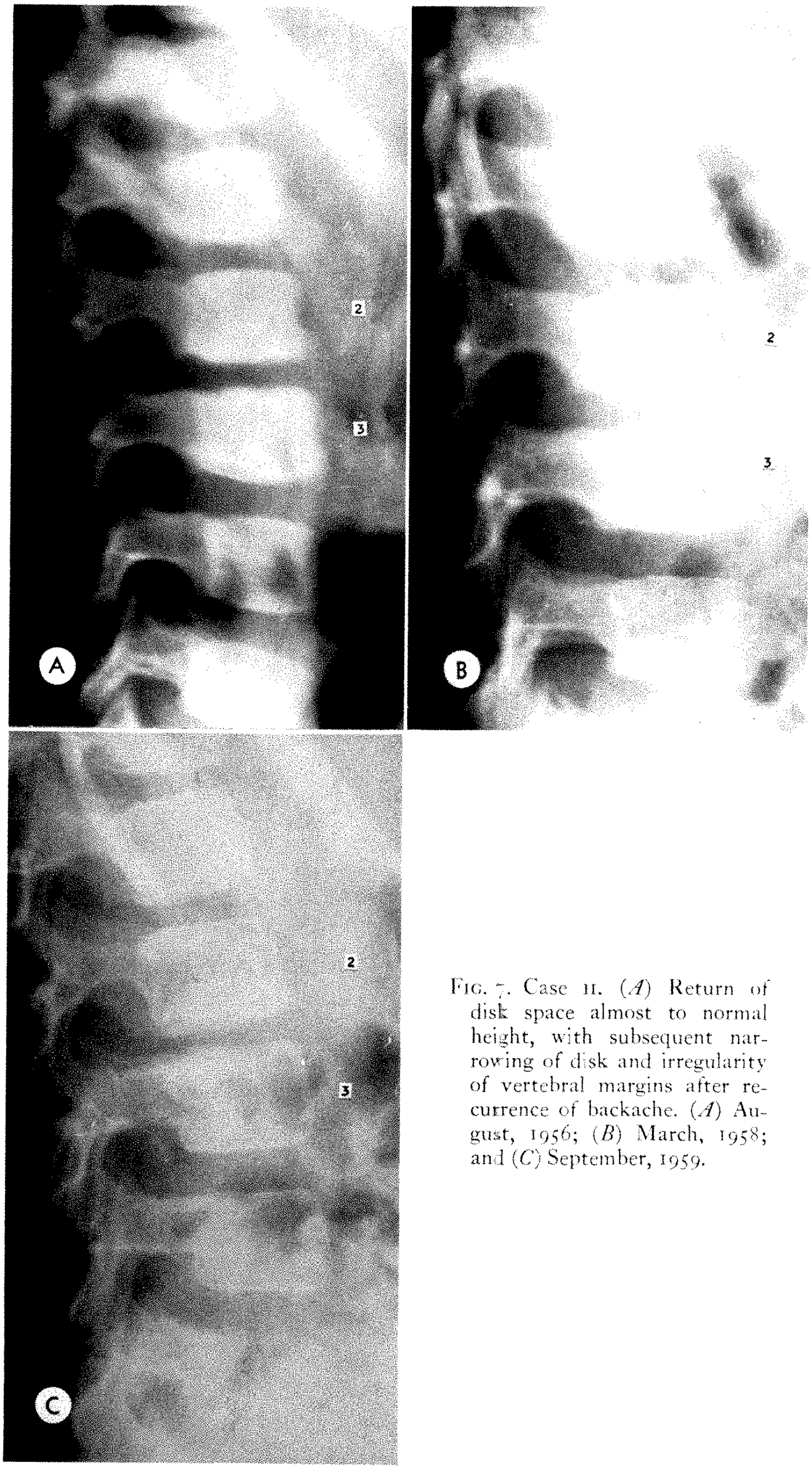

Fig. 7. Case II. (*A*) Return of disk space almost to normal height, with subsequent narrowing of disk and irregularity of vertebral margins after recurrence of backache. (*A*) August, 1956; (*B*) March, 1958; and (*C*) September, 1959.

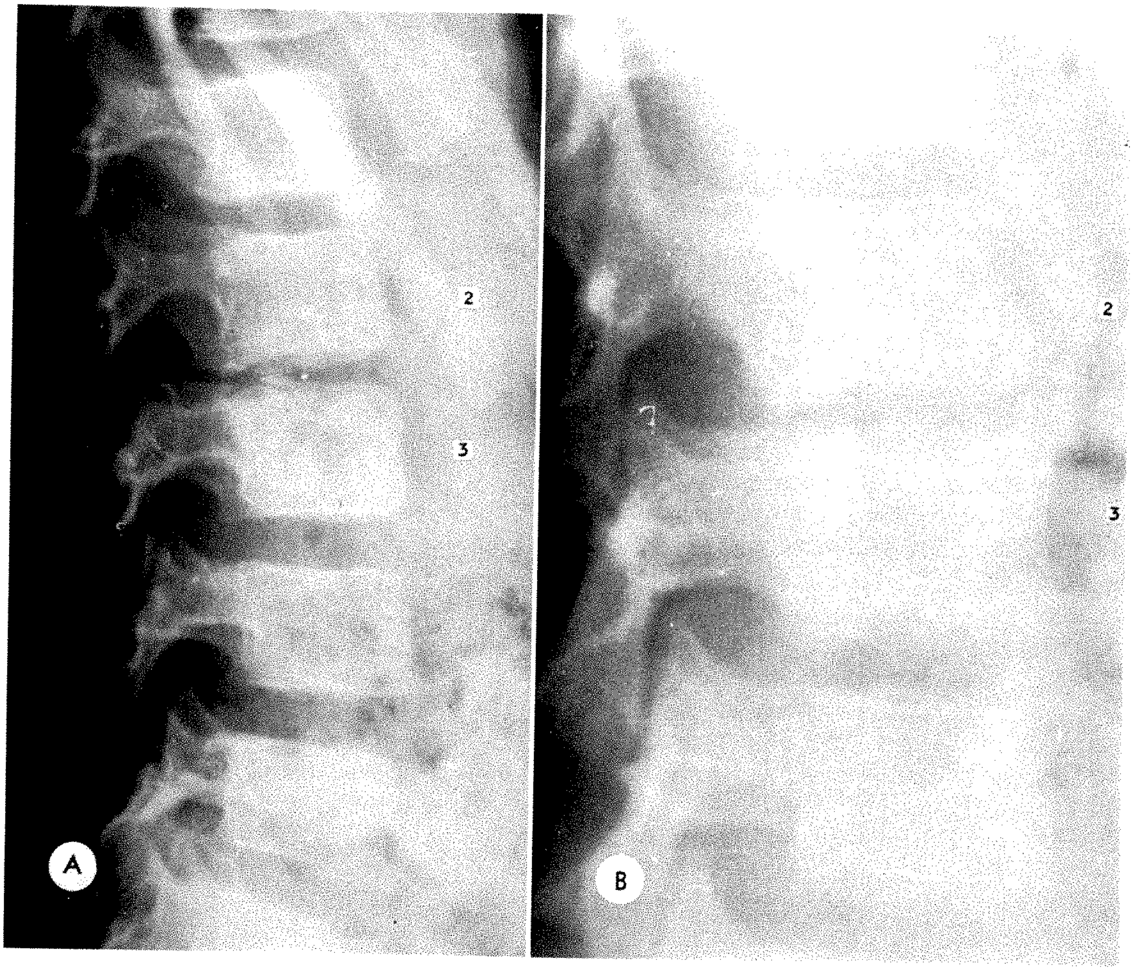

FIG. 8. Case II. Further follow-up examination showing no change. (*A*) March, 1961; and (*B*) June, 1962.

Infectious spread via venous pathways must also be considered. Batson[1] has described the venous plexus connecting the pelvis, abdomen and thorax with the spine. Wiley and Trueta[20] have shown that tributaries from the metaphysis of the vertebral body are collected into large valveless channels in the spongiosa. It is therefore possible for the process to begin within the disk, though actual proof of this is lacking. On the other hand the primary process may start in the vertebral body adjacent to the cartilage end plate with subsequent extension through the plate into the disk.

Seven of the cases in our series gave a history of trauma. This incidence would appear to be too high to be regarded as coincidental. Wilensky[19] states that trauma may injure a vessel and this in the presence of bacteremia could help localize an infection. In none of the cases was the trauma severe and the period until the onset of symptoms ranged from 3 days to 4 weeks.

DIFFERENTIAL DIAGNOSIS

Differentiation between spondylarthritis and tuberculosis can be extremely difficult if not impossible roentgenologically. The fact that the site of predilection is the lower thoracic spine with tuberculosis, while in spondylarthritis the lumbar region is favored, may be of some aid. As has been pointed out by Doub and Badgley[5] and others, tuberculosis can show narrowing of the disk as the earliest change. Therefore, a knowledge of the history, laboratory find-

Table II

TYPES OF TREATMENT

Plaster jacket—3 cases
Fracture boards—1
Plaster half-shell—1
Bradford and Whitman frame—1
Plaster jacket and antituberculin drugs—1
Whitman frame, Taylor brace, and sulfathiazole—1
Plaster jacket and penicillin—2
Plaster jacket, penicillin and chloromycetin—1
Plaster jacket, and erythromycin—3
Plaster jacket, erythromycin and chloromycetin—6

ings and progress is essential in arriving at a correct diagnosis. Spondylarthritis usually presents with an acute onset and roentgenologic changes are frequently noted at the time of the initial examination, which militates against tuberculosis. The tuberculin test is negative. The progress of the condition is more rapid than with tuberculosis and there tends to be less bone destruction with much earlier reconstitution of the affected vertebrae.

Spinal osteomyelitis caused by Salmonella or Brucella is uncommon. The roentgenologic changes may be indistinguishable from those of spondylarthritis. Kulowski and Vinke[13] suggest that in brucellosis destruction of the articular facets is present in the lower lumbar region, which is not a feature in spondylarthritis. A positive blood agglutination test will help to make a definite differentiation.

In the older child osteochondritis of the spine must also be considered. The generalized type (Scheuermann's disease) shows disk space narrowing with irregularity of the adjacent vertebral margins and a tendency for the bodies to be wedged anteriorly. This usually involves more than one vertebral level in the lower thoracic and upper lumbar area. The localized type may present more difficulty as one or several levels may be affected. There is frequently disk narrowing and a defect at the anterior vertebral angle is seen which has a fairly well defined punched out appearance. The patient may complain of back or hip pain; however, the sedimentation rate is normal in cases of osteochondritis. The localized type is usually seen in the older child, although a case which seems to represent this condition is reported in a 4 year old girl by Ekengren and Lindblom.[8]

TREATMENT

Table II shows the types of treatment carried out in our 20 patients. During the acute phase some form of back support was employed. Thirteen patients received antibiotic therapy, usually for 3 weeks, 6 had none, while 1 was given antituberculin drugs. This resulted in improvement of symptoms in all cases. Antibiotics do seem to hasten relief of pain in the early stage of the disease, especially in those who are moderately ill, though their role in the final outcome of the disorder is questionable. No difference could be found during the follow-up in those who did or did not receive antibiotics. The duration from the onset until the patient was symptom free without back support averaged $2\frac{1}{2}$ months. The patients have been followed for $2\frac{1}{2}$ months to 6 years and 2 months and in only 2 instances has there been an apparent recurrence of symptoms, 1 and 4 years respectively after the primary process had subsided.

SUMMARY

Spondylarthritis is a spinal disorder, occurring primarily in infants and young children, which appears to be inflammatory in nature. It presents fairly typical clinical and roentgenologic findings. Five of the 20 cases presented were biopsied with pyogenic staphylococcus being cultured in 2. The course is relatively rapid and usually leads to complete recovery clinically.

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STRESS FRACTURE OF THE TIBIA IN CHILDREN

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FATIGUE or stress fracture of the tibia has been well documented in the literature, occurring chiefly in armed service recruits, ballet dancers and athletes. In this report 5 cases are described which occurred in boys between the ages of 7 and 13 years. Emphasis is placed on the symptom of pain on weight bearing and absence of pain at rest. This finding, common to all 5 cases, serves as an important and distinctive point in the differential diagnosis of this condition. Extensive roentgenologic and laboratory examinations can be avoided, if the correct diagnosis of stress fracture is made. It is mandatory that close correlation of the clinical findings, roentgenographic studies and a high index of suspicion exist in order to distinguish readily this type of fracture from more serious entities.

REVIEW OF THE LITERATURE

In 1937, Ollenquist[9] first described march fractures of the tibia occurring in Finnish army recruits. He termed the condition "osteopathia itineraria tibiae." Roberts and Vogt,[10] in 1939, reported 12 cases of stress fracture of the tibia in children between 4 and 16 years of age (2 girls and 10 boys). One of the girls had both tibias involved. In 1942, Hartley[4] reported 14 cases of stress fracture of the tibia; 3 patients with bilateral fracture. He added 1 more case in 1943.[5] His reports were of patients between the ages of 7 and 20 years. Krause and Thompson,[7] in 1943, described 4 cases of stress fracture of the tibia in army recruits, with age levels between 21 and 28 years. In 1945, Mann[8] reported 3 cases of fatigue fracture of the tibia in naval trainees between the ages of 18 and 20 years. In the same year, Wolfe and Robertson[14] wrote a review article on fatigue fracture of the tibia and added 1 case of a naval recruit (aged 15). Kelly and Murphy[6] added 2 cases, ages 14 years, in 1951. In 1954, Singer and Maudsley[11] reported 5 cases of fatigue fracture of the lower tibia and made note that the upper third is the commonest site of occurrence. In 1956, Burrows[2] added 4 cases of fatigue infraction of the middle third of the tibia in ballet dancers. In 1959, Wang, Lowrey and Severance[13] reported 8 cases with fatigue fracture of the tibia. Devas,[3] in a literature review, listed 78 cases from the reports printed from 1938 to 1958. He added 16 cases which occurred in athletes between the ages of 15 and 27. Sponsel and Udasco,[12] in 1958, reported 1 case of a 10 year old boy with upper tibia fracture and 1 case of a 62 year old female with fatigue fractures of the lower third of the tibia and fibula. Benedict,[1] in 1959, gave an excellent report and analysis of 35 Marine trainees with this condition.

INCIDENCE

A review of the literature indicates that the majority of cases was found in youths of armed service recruit age. The finding of 5 cases in 2 years in children between the ages of 7 and 13 years, in a population area of 90,000, suggests that this is a much more common entity than the existing reports indicate. Hartley[5] states that fatigue fracture occurs 7 times more frequently in the metatarsals than in the tibia, but the disease is seen 5 to 6 times more frequently in the tibia than in the femur or fibula. He notes that fatigue fracture occurs only occasionally in the os calcis or pelvis. In children, the most common site of occurrence in the tibia is in its proximal third. Devas[3] noted that of the 78 cases he found in the literature, 65 involved the proximal third of the tibia. In his own 16 cases, 1 occurred in the proximal third. It occurs most often in boys, with no predilection for one leg over the other. The age levels reported are from 4 to 28 years, except for the cases reported by Singer and Maudsley,[11] and 1 case by Sponsel and Udasco,[12] which were in the distal third and in patients between the ages of 45 and 69 years.

THEORY OF CAUSATION

Wolfe and Robertson[14] suggest that, similar to the way by which metal can be fractured by bending it back and forth, the rhythmically repeated mechanical stress at the point of greatest bone bending can produce fracture of individual trabeculae. Crystallization occurs in metal at the point of fracture, and the same process has been shown by the electron microscope to occur at the stress fracture site in bone.

Hartley[4] believes that the condition is a fatigue fracture, due either to faulty crystal structure of bone at this area of maximum strength or to abnormal stress at a site already subject to considerable strain, or to a combination of both.

Mann[8] proposes that muscle fatigue consequent to unaccustomed or exceptional exertion is probably an important contributory factor. The loss of normal tone in the leg muscles leaves the bone to bear the brunt of "mechanical insult." He, too, indicates that infractions of bone are analogous to fatigue fractures occurring in metals subjected to repeated stresses.

HISTORY AND PHYSICAL FINDINGS

Absence of any injury and the invariable complaint of pain on weight bearing, but relief of pain on sitting or lying, provided the constant features in the history. The pain on weight bearing was a persistent dull type, occurring in the calf or near the upper end of the tibia toward its medial side. Upon walking or running, the children complained variably of a sudden severe pain or just stiffness with distinct increase in pain over that present when merely weight bearing. The positive physical findings were local tenderness on one or both sides of the tibial crest with several children showing local edema, increased warmth and palpable callus. There was no rise in temperature in any of the cases; a limp was present in all. A period of 3 to 8 weeks elapsed from the onset of pain until the patient first appeared for examination.

ROENTGENOGRAPHIC FINDINGS

The roentgenographic changes occur from 3.5 to 9.0 cm. below the epiphyseal line of the proximal end of the tibia. Roentgenograms made in the first week from the onset of pain may show a faint line of periosteal new bone posteriorly, medially and laterally. Hartley[4] has suggested that a "nick" in the cortex is most often noted at this time. The roentgenograms made in the second and fourth weeks after the onset of pain, show a band of condensation traversing the posterior cortex of the bone, which in the lateral projection extends anteriorly, either in a "U" or "V" shape to the intramedullary portion of the shaft, and in some instances, extends in a more narrow pattern, obliquely across to the anterior cortex, forming a "Y" shape. Variably, there may be a short hairline fracture extending anteriorly from the posterior cortex, for a distance of 1 to 3 cm., beginning with a "nick" at the edge of the cortex. The periosteal new bone becomes thicker on the posterior, medial and lateral aspects of the shaft, and as weeks pass, the bone becomes fusiform in appearance in the proximal third. In the literature the prominence of the "nick" formation and the invariable finding of the fracture line are stressed, but this was not a prominent finding in these cases, possibly because of the delay in the patients appearing for examination. Devas[3] reported that a fracture sometimes was not visible on the roentgenograms until 3 months after the onset of symptoms.

DIFFERENTIAL DIAGNOSIS

1. *Sprain.* Stress fracture of the tibia may exhibit the same early signs and symptoms as a sprain, but roentgenographically, the two are easily distinguished by the presence of periosteal new bone formation and occasionally a fissure fracture line in the posterior or medial cortex.

2. *Sarcoma.* The lack of bone destruction and the regular buttress of periosteal new

bone formation serve to help distinguish stress fracture from a sarcoma, roentgenographically. In sarcoma, the presence of continuous pain and local swelling differs from the lack of pain at rest, and slight or lack of swelling in stress fracture. The relatively short period necessary to observe new bone formation in stress fracture provides further differentiation from sarcoma.

3. *Osteitis.* Pain and limp are symptoms common to both, but the pain in stress fracture occurs only on weight bearing.

4. *Looser's Umbauzonen.* This entity is always associated with advanced generalized bone disease. The changes remain static in contrast to the rapid progression of callus formation in stress fracture.

PROGNOSIS AND TREATMENT

Immobilization in a plaster cast for several weeks followed by gradual increase in activity and weight bearing serve to promote complete spontaneous healing within 8 to 12 weeks. No residual deformity, other than thickening of the cortex will result.

REPORT OF CASES

CASE 1. D.E., an 11 year old boy, developed pain in his left leg 5 weeks prior to the time when the first roentgenograms were made on May 2, 1958 (Fig. 1, *A* and *B*). No history of injury was elicited. The pain was present only on weight bearing and was absent at rest. Past history was noncontributory. Physical examination showed slight swelling over the proximal aspect of the left tibia with increase in warmth over the swollen part. The initial impression was Ewing's sarcoma. Multiple studies, including serology, blood protein determination, sedimentation rate, antistreptolysin titer, alkaline phosphatase, phosphorus, calcium, white blood cell count, red blood cell count, hematocrit, and agglutination titers for typhoid, paratyphoid and Brucella were within normal range. Biopsy of the left tibia was done on May 20, 1958. At surgery, the periosteum was found to be thickened and lifted, while the

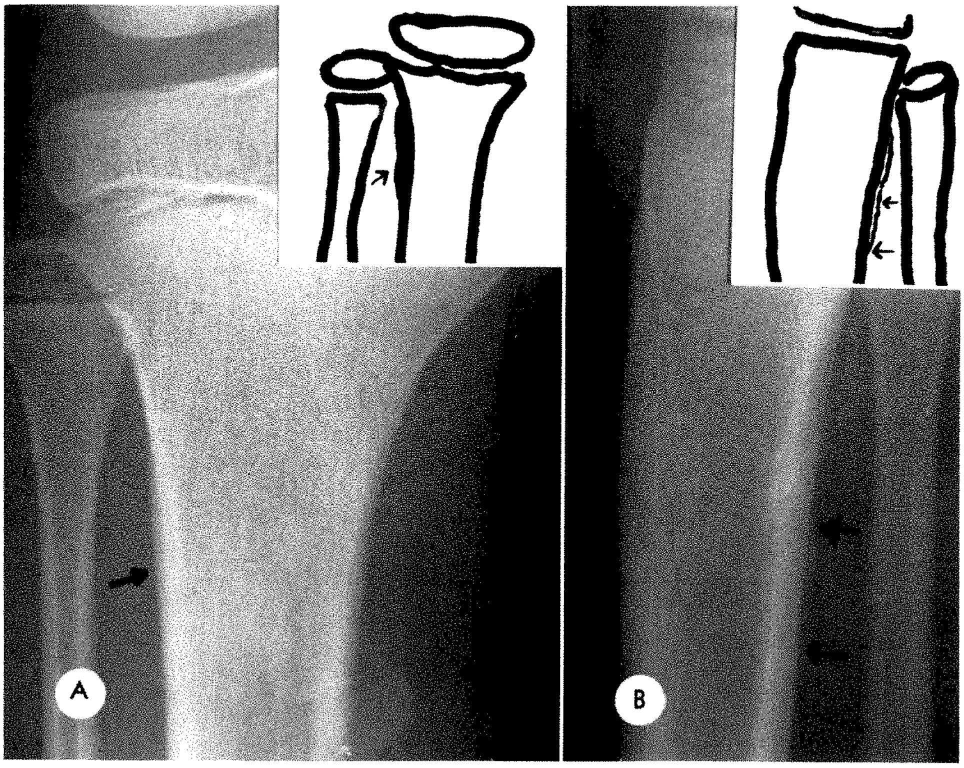

FIG. 1. Case 1. (*A* and *B*) May 2, 1958: A thin layer of periosteal new bone is seen laterally and posteriorly. No fissure fracture is visible.

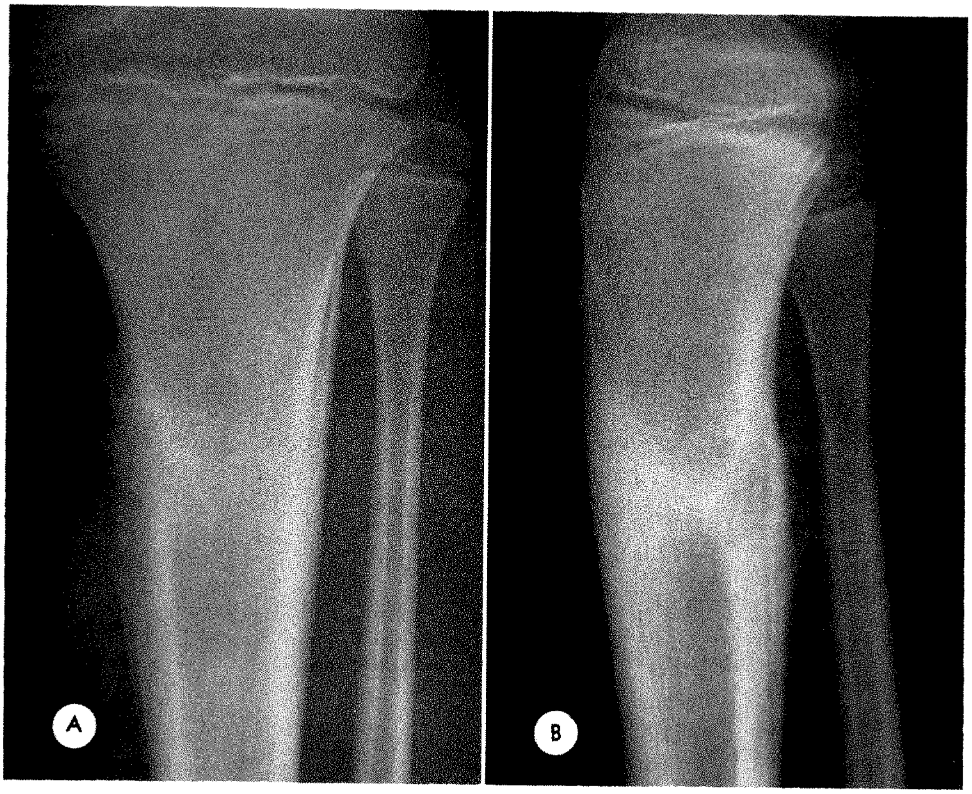

Fig. 2. Case i. (*A* and *B*) June 23, 1958: A broad band of bone condensation is seen across the posterior cortex with callus production laterally, medially and posteriorly. The irregularity seen medially is at the site of biopsy taken May 20, 1958.

underlying bone appeared to be soft. The periosteum was incised and dissected. A portion was taken for biopsy and then a block of bone was removed from the "tumor site." The pathologic diagnosis was: periostitis, focal, chronic. Further roentgenograms, made on June 23, 1958 (Fig. 2, *A* and *B*) and April 15, 1960 (Fig. 3, *A* and *B*), showed a broad band of bone condensation across the posterior cortex, callus production and a thickened cortex. All pain on weight bearing disappeared within 2 months after the biopsy procedure.

Case ii. G.B., an 11 year old boy, 2 months previous to the roentgenographic studies made on May 27, 1958 (Fig. 4, *A* and *B*) began to have pain in his left leg below the knee on weight bearing or walking. The area showed slight swelling and redness according to the parents. Physical examination revealed slight

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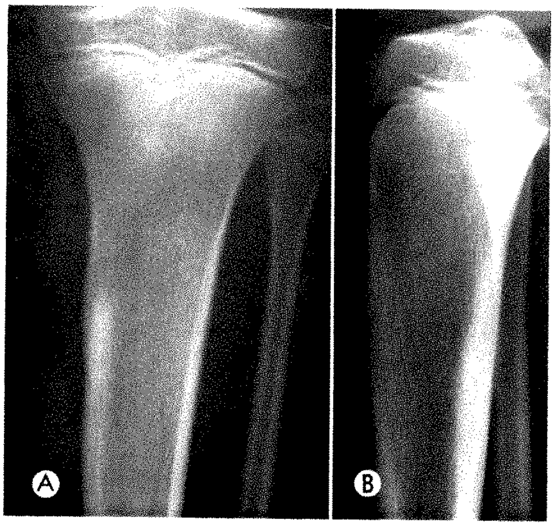

Fig. 3. Case i. (*A* and *B*) April 15, 1960: A thickened cortex is seen at the site of the stress fracture and the biopsy site.

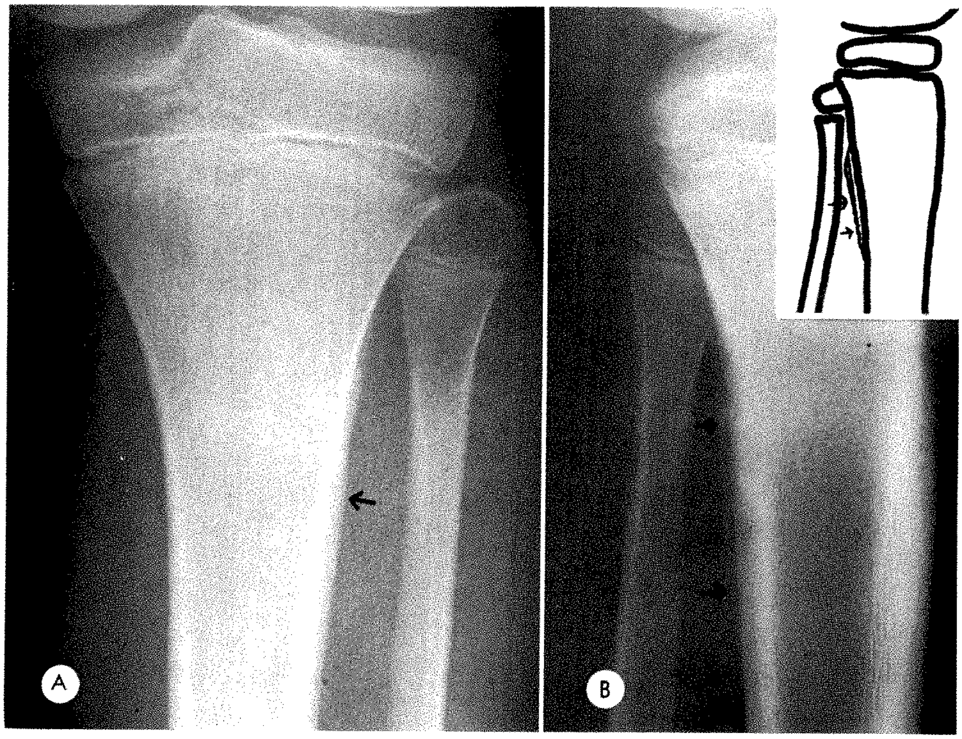

FIG. 4. Case II. (*A* and *B*) May 27, 1958: Periosteal new bone formation is seen laterally and posteriorly with an area of condensation posteriorly.

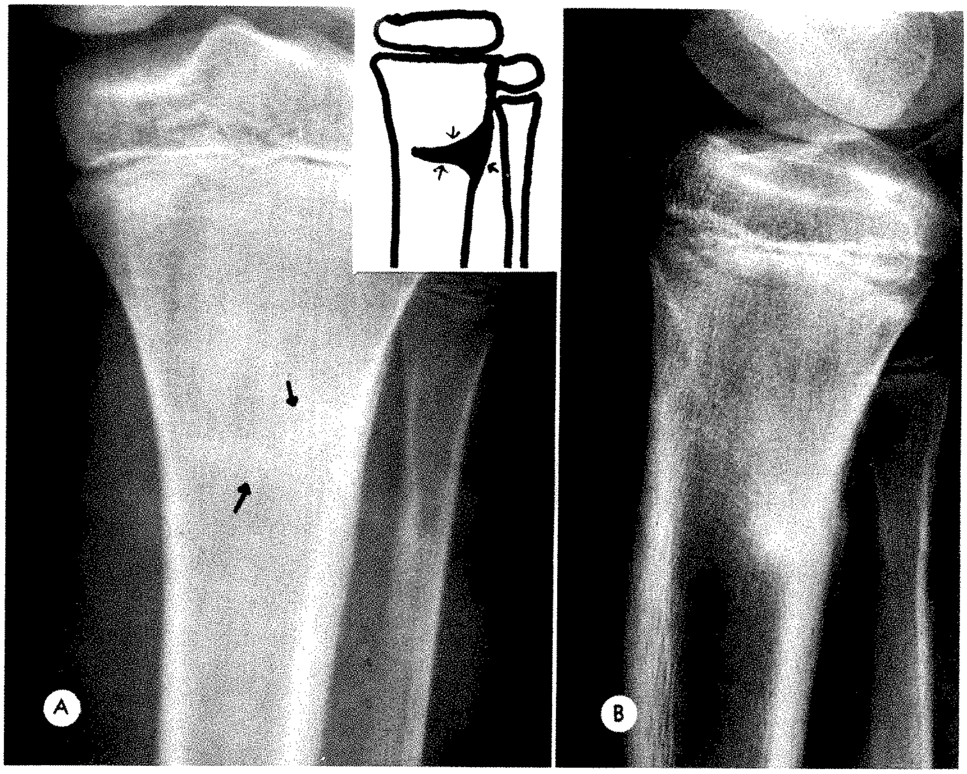

FIG. 5. Case II. (*A* and *B*) June 6, 1958: A band of bone condensation is seen across the shaft in the posterior cortex. There is also thickening of the callus laterally and posteriorly and a short radiolucent hairline extending anteriorly through the posterior cortex.

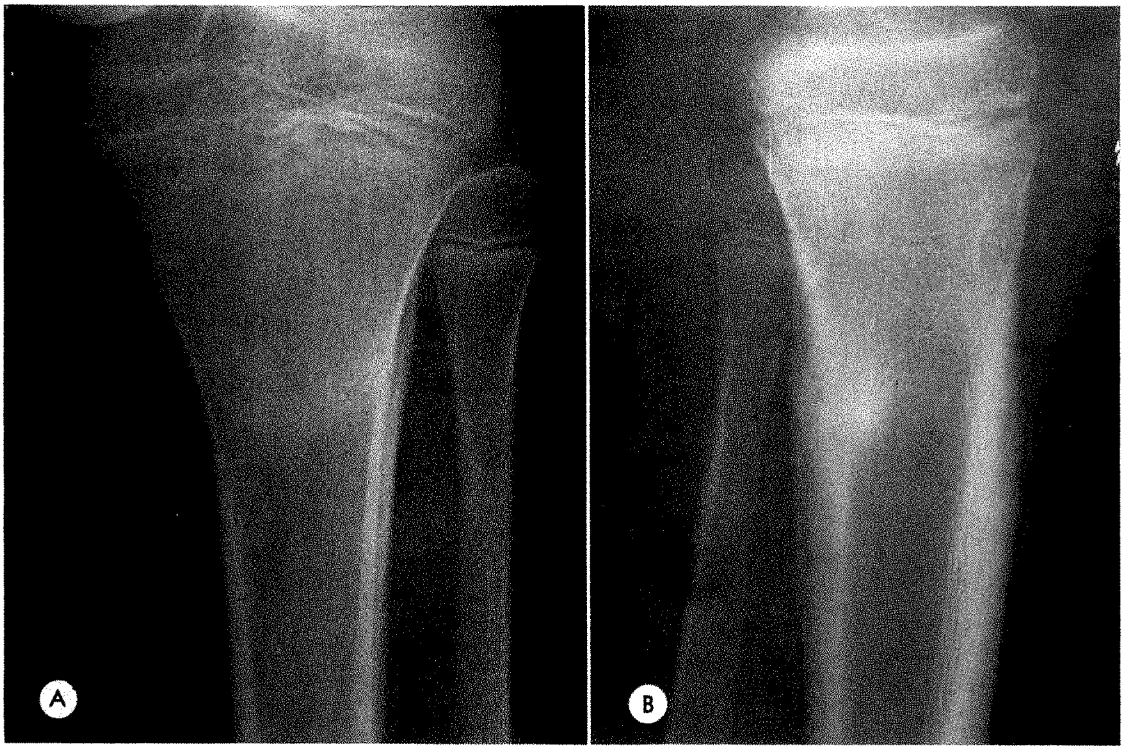

Fig. 6. Case II. (*A* and *B*) June 27, 1958: A U-shaped area of condensation is seen extending anteriorly from the posterior cortex. There is further production of callus posteriorly and laterally and disappearance of the posterior "nick."

swelling of the proximal third of the left leg. No appreciable tenderness was elicited. The clinical impression was periostitis or osteomyelitis of the left tibia. Blood studies included sedimentation rate, complete blood cell count, hematocrit and serology, all of which were normal. Roentgenograms made on June 6, 1958 (Fig. 5, *A* and *B*) and June 27, 1958 (Fig. 6, *A* and *B*) showed a band of condensation across the shaft in the posterior cortex and callus production. One month after the last roentgenographic studies were made, all pain on weight bearing disappeared.

Case III. C.Z., an 8 year old boy, 1 month prior to the time that the first roentgenograms were taken on June 6, 1958 (Fig. 7, *A* and *B*), experienced pain in the calf of his right leg while standing or walking. There was no history of injury. A physical examination showed no local swelling. The clinical impression was that a bone tumor should be ruled out. Further roentgenograms, including a skeletal survey and laminagrams of the right tibia on June 17, 1958 (Fig. 8, *A* and *B*) and June 18, 1958 (Fig. 9, *A* and *B*), showed formation of periosteal new bone, extension of condensation across the shaft and a minute fissure in the posterolateral cortex. Multiple blood studies were all normal. Orthopedic observation continued, and due to the characteristic course of the clinical improvement, no biopsy was made. Roentgenograms on April 19, 1960 (Fig. 10, *A* and *B*) showed only slight residual cortical thickening posteriorly.

Case IV. J.C., a 13 year old boy, developed pain in his left leg 3 weeks prior to his first roentgenographic examination on March 16, 1960. History revealed increasing pain in the upper calf of his left leg, especially when walking or running, but no injury. Physical examination showed slight bony enlargement over the medial aspect of the tibia, 3 to 5 inches below the joint space. The circumference was ½ inch greater than that of the right leg at this point. There was tenderness on pressure, but no warmth was noted. The clinical impression was a possible tumor or an old subperiosteal hemorrhage. Multiple blood chemistry studies showed no abnormalities. The patient showed progres-

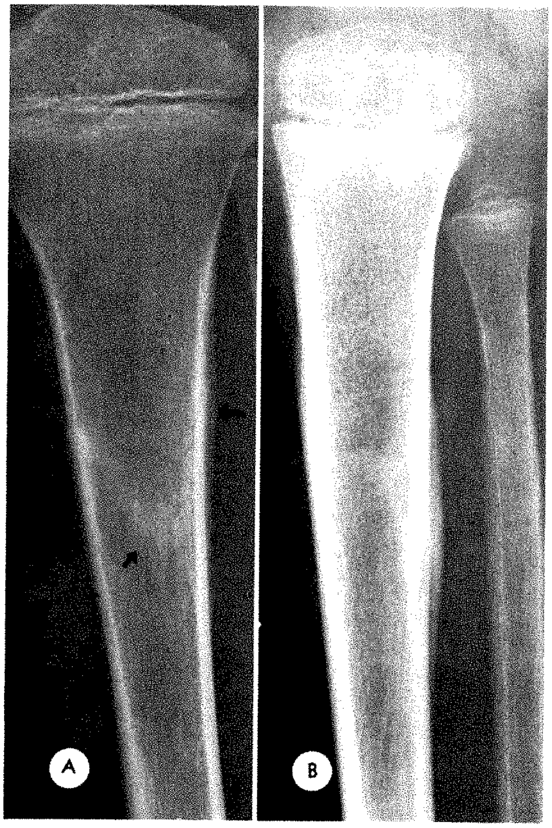

Fig. 7. Case III. (*A* and *B*) June 6, 1958: A line of periosteal new bone formation is seen extending 4.0 cm. along the shaft, posteriorly and medially. There is a triangular zone of bone condensation projecting anteriorly and laterally across a portion of the cortex.

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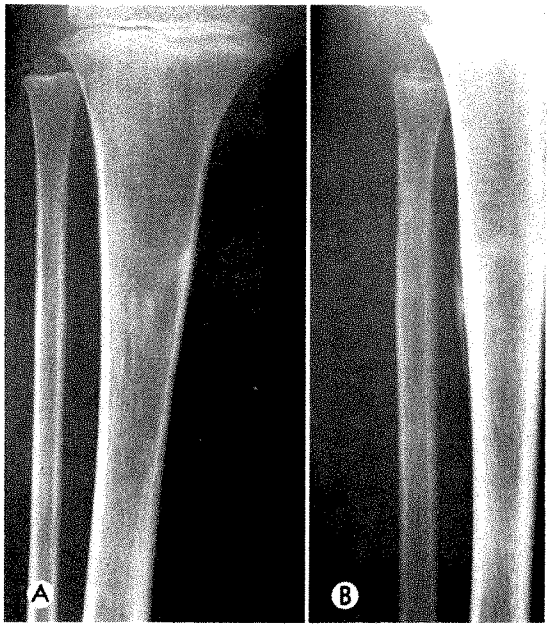

Fig. 8. Case III. (*A* and *B*) June 17, 1958: Further formation of periosteal new bone and extension of oblique zone of condensation across the shaft are seen.

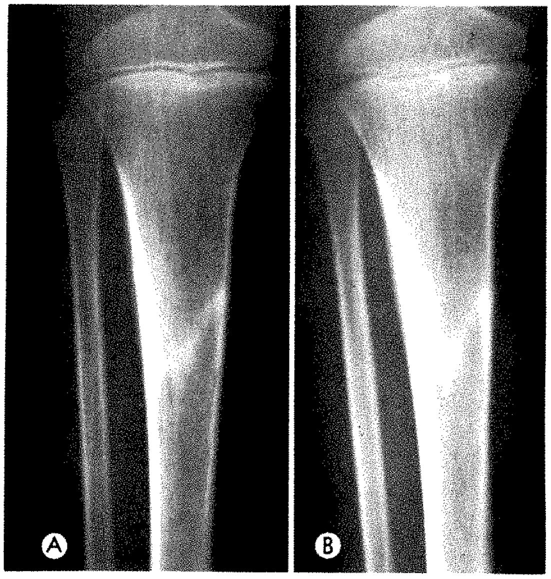

Fig. 9. Case III. (*A* and *B*) June 18, 1958: Laminagrams show a minute fissure in the posterolateral cortex.

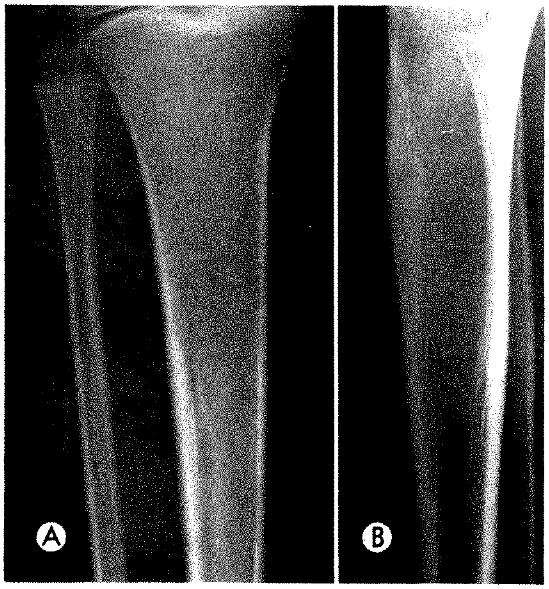

Fig. 10. Case III. (*A* and *B*) April 19, 1960: There is practically no residual cortex change.

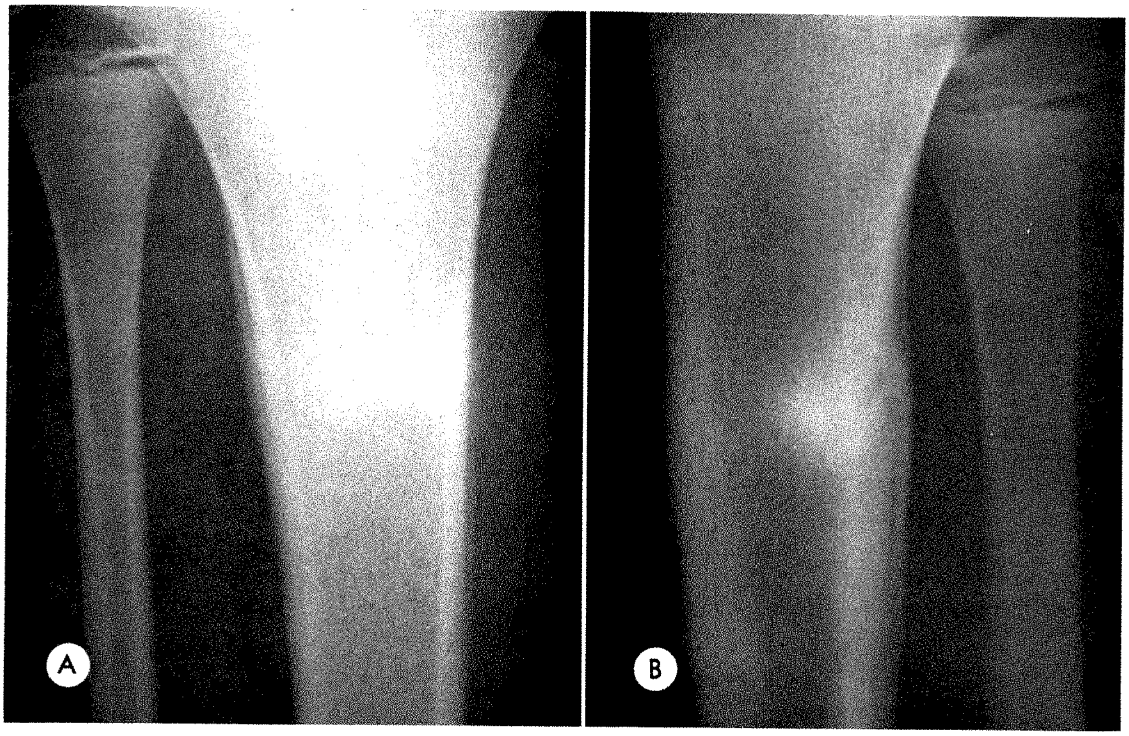

Fig. 11. Case iv. (*A* and *B*) April 5, 1960: Formation of callus is seen posteriorly, medially and laterally. A U-shaped zone of bone condensation extending anteriorly from the posterior cortex and a short "nick" or fissure-like radiolucent line in the posterior cortex extending anteriorly are also demonstrated.

sive clinical improvement with bed rest. Roentgenograms on April 5, 1960 (Fig. 11, *A* and *B*) showed callus formation. Pain on weight bearing disappeared 1 month later.

Case v. C.Z., a 12 year old boy, complained of pain on weight bearing 3 weeks prior to a roentgenographic study made on May 25, 1960 (Fig. 12). The pain was confined to the upper calf of his right leg. There was no pain while at rest. There was no history of injury. The roentgenographic impression was stress fracture of the tibia. The leg was placed in a plaster cast. The patient took off his own cast 1 month later and did not return for further roentgen studies.

SUMMARY

Five cases of stress fracture of the tibia in boys between the ages of 7 and 13 years are

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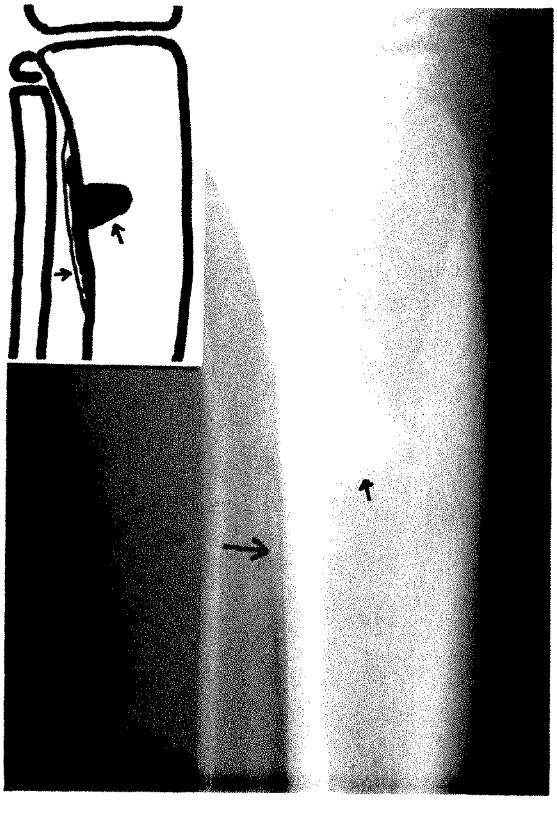

Fig. 12. Case v. May 25, 1960: Periosteal new bone formation is seen posteriorly. There is also a V-shaped zone of condensation extending anteriorly.

presented. The finding of 5 cases in 2 years in a population area of 90,000 suggests that this disease is more common in children than the reports in the literature indicate. The similarity between metal and bone, when subjected to repeated mechanical stress or bending, supports the crystallization theory of causation. The importance of the clinical finding of pain on weight bearing and absence of pain at rest is stressed in differentiating this disease from the other more serious entities. The characteristic roentgen findings of stress fracture of the tibia are progressive formation of periosteal new bone, zone of bone condensation chiefly in the posterior cortex, and the variable appearance of a short hairline fracture. The time interval from the first roentgen changes to complete healing is 3 to 5 months. Treatment consists of simple immobilization.

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The author wishes to express his appreciation to Dr. Harry Hauser and Dr. D. A. Russell, for their helpful suggestions, and to Dr. Joseph Strong and Dr. George Bennett for permission to use their cases.

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Vol. 91, No. 3

THE ABSENCE OF LEAD LINES IN BONES OF CHILDREN WITH EARLY LEAD POISONING

By PEGGY SARTAIN, M.D.,* JO ANNE WHITAKER, M.D.,* *and* JANET MARTIN, M.D.†
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FAILURE to demonstrate lead lines in children with early lead poisoning does not rule out this diagnosis.

Around 1930 several American[2,12,14,19,20] and Japanese[9,10,17] workers demonstrated that a recognizable metallic band appeared at the ends of growing bones in infants and children absorbing appreciable amounts of lead. Since that time the roentgenographic demonstration of these transverse bands has been considered to be one of the most significant signs for the diagnosis of lead poisoning.

This report presents data showing that lead lines are absent in most cases of early lead poisoning. For this reason, and also because heavy transverse bands may be found in apparently normal children, we agree with Caffey's[5] statement that roentgen findings must be given secondary consideration when making the diagnosis of lead poisoning.

PROCEDURE AND PATIENT MATERIAL

Lead poisoning was diagnosed by the usual clinical manifestations and laboratory determinations and confirmed by the versenate diagnostic test.[21]

There is an overlapping of values for urinary lead in normal children and those with lead poisoning. Nelson's[11] textbook of pediatrics gives normal values for urinary concentration of lead as zero to 400 μg./l.; the values for children with lead poisoning range from 35 to 720 μg./l. It is the policy at this institution to hospitalize all children with pica and basophilic stippling (whether or not there are other signs of lead poisoning) and subject them to the versenate diagnostic test. Urine is collected for 24 hours prior to the administration of edathamil calcium disodium (versenate) and during the 24 hours of versenate administration (75 mg./kg. intramuscularly, divided into three doses at 8 hour intervals). If the diagnostic test demonstrates an excretion of lead in the second urine specimen of more than 500 μg./l., there has been excessive ingestion of lead-containing substances.

Roentgenograms of the long bones of 31 children with lead poisoning and 17 control children from the Parkland Memorial Hospital and the Children's Medical Center, Dallas, Texas, were compared. The 48 unlabeled roentgenograms were evaluated independently by Dr. Janet Martin (Assistant Staff Radiologist, Children's Medical Center, Dallas) and Dr. John Caffey (Professor of Pediatrics, University of Colorado Medical Center, Denver). Their interpretations were compared with the initial readings of the hospital's radiology staff.

The control children were hospitalized for a variety of conditions. All had normal versenate diagnostic tests. Thirteen of the 17 controls had iron deficiency anemia.

It is difficult to separate early lead poisoning from late lead poisoning, unless, of course, encephalopathy is present. A child who has been ingesting lead-containing substances for only a short period of time may have many of the symptoms and signs associated with plumbism, while another may have only mild involvement after many months. For the purpose of this report, the lead poisoning cases were divided into early and late cases on the basis of their pre-versenate urinary lead levels. All children with levels of less than 35 μg./l.

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were included in the early lead poisoning group. All children with levels of 35 µg./l. or more or who had evidence of encephalopathy were included in the late group.

RESULTS

The interpretations of the 3 observers are shown in Table I.

Seventeen patients were placed in the late lead poisoning category. Their ages ranged from 14 months to 4 years with an average age of 2 years. This group included 8 patients with symptoms and signs of encephalopathy. Of the 17 roentgenograms, only 2 were read as positive by all 3 observers. Seven roentgenograms were read as positive or borderline by 2 observers, and 3 were read as positive or borderline by 1 observer. Five were called normal by all 3 observers.

There were 14 patients in the early lead poisoning group. Their ages varied from 9 months to 4½ years with an average age of 20½ months. One roentgenogram was read as positive by 1 observer and borderline by 2 observers, and 1 was called positive by 1 and borderline by 1 observer. Two were read as positive by 1 observer. Ten were called normal by all 3 observers.

The 17 control patients ranged in age from 10 months to 5 years (average age 19 months), except for 1 child of 13 years. Fourteen of the roentgenograms were called normal by all 3 observers. Two were reported as borderline by one observer. The remaining roentgenogram was read as positive by 2 observers. This was of a 20 month old white female with poliomyelitis (Type I virus isolated from stool) who developed residual paralysis. This child had a history of pica and constipation. She had a microcytic hypochromic anemia (which responded to iron therapy) without basophilic stippling. The urine was negative for coproporphyrin. A flat roentgenogram of the abdomen revealed one fleck of radiopaque material in the region of the cecum. A 24 hour urine specimen before versenate was reported as 89 µg./l. Following administration of versenate, she excreted 424 µg./l. of lead. These levels are equivocal; and, although she was proved to have poliomyelitis, further examination should be done to determine if she had coexisting plumbism.

COMMENT

Symptoms and laboratory manifestations associated with lead poisoning are shown in Table II.

The symptoms of lead poisoning are often vague and may simulate other conditions. Pica is almost invariably a symptom of children with lead poisoning; however, other symptoms such as vomiting, consti-

Table I

COMPARATIVE EVALUATION OF ROENTGENOGRAMS

Patient Group	No. of Patients	Initial Interpretation	No. of Roentgenograms	Dr. Martin's Interpretation			Dr. Caffey's Interpretation		
				positive	borderline	normal	positive	borderline	normal
Late Lead Poisoning	17	positive	7	2	0	5	4	1	2
		borderline	1	0	1	0	0	0	1
		normal	9	2	2	5	3	0	6
Early Lead Poisoning	14	positive	2	0	1	1	0	1	1
		borderline	0	0	0	0	0	0	0
		normal	12	0	1	11	2	0	10
Controls	17	positive	1	1	0	0	0	0	1
		borderline	1	0	0	1	0	0	1
		normal	15	0	1	14	0	0	15

TABLE II

INCIDENCE OF SYMPTOMS AND LABORATORY FINDINGS ASSOCIATED WITH LEAD POISONING

Patient Group	No. of Patients	Symptoms Per Cent of Patients						Blood Studies Per Cent of Patients					Findings in Urine Per Cent of Patients			Cerebrospinal Fluid Per Cent of Patients		Roentgenograms Per Cent of Patients	
		pica	vomiting	constipation	lethargy	irritability	convulsions	Hb <10 gm. %	hypochromia	polychromasia	basophilic stippling	+fluorescyte prep.	sugar	albumin	coproporphyrin	cells	protein >50 mg. %	lead lines	abdomen
Late Lead Poisoning	17	100	41	23.5	18	23.5	35	88	93	100	100	52	6	29	12	25	25	45	40
Early Lead Poisoning	14	86	7	29	29	7	0	86	93	86	85	43	7	21	23	0	0	17	33
Controls	17	53	47	12	29	23.5	6	82	82	71	41	6	12	23.5	7	40	20	8	10

pation, lethargy and irritability may not be present.

The classic anemia with polychromasia, hypochromia, microcytosis, and basophilic stippling suggests the diagnosis of plumbism, but may appear only after irreversible damage has occurred. In our experience the "fluorescyte prep"[22] has been a valuable aid in the rapid diagnosis of lead poisoning, but is only of questionable use when anemia is not present. Sugar and protein may be present in the urine on the basis of renal damage. Increased concentration of coproporphyrin in the urine is often found. When present, these laboratory findings are helpful, but the diagnosis cannot be ruled out in their absence. The demonstration of radiopacities in the abdomen is also helpful in some cases.

With encephalopathy there may be elevation of the total protein and occasionally of the blood cell count and pressure of the cerebrospinal fluid.

DISCUSSION

Of the many available descriptions[2,5,6,14,16,19,20] of the skeletal changes associated with lead poisoning, the most classic is that of Park and colleagues.[13]

The ability of organic bone to absorb and deposit the salts of calcium and phosphorus creates their contrasting appearance from other tissues on roentgenograms.

The factors necessary for the production of transverse bands of increased metaphyseal density in the bones of patients with lead poisoning are rapidly growing bones and the deposition of appreciable quantities of lead and calcium salts. Adult humans[1] and dogs[2] do not develop lead lines. Children with rickets do not have lead lines until healing begins and mineral is deposited in the bone.[4,19]

Lead lines vary in width but can be as much as 5 mm. wide. They rapidly acquire a chalk-like whiteness and can be accompanied by a parallel line of similar density separated by a few millimeters of more normal appearing bone. They are most readily found in the fastest growing bones—anterior ends of ribs, and in the iliac crests.

In children with growing bones and available calcium, the time of appearance of lead lines is dependent upon the amount of lead ingested and the metabolic activity of the bones. It should be remembered, however, that they are not generated rapidly enough to be visualized during the earliest phase of lead poisoning and that they form more slowly in older children.[5] Toxicity may intervene before roentgenograms are diagnostic. It requires approximately 3 months for lead lines to appear after the inhalation of lead, and up to 6 months when lead is ingested.[6]

Only 17 per cent of patients with early lead poisoning had positive or borderline roentgenograms, compared with 45 per cent of the late cases. Four of the 8 children with lead encephalopathy had normal bone roentgenograms.

With prolonged and chronic exposure to lead, bands of increased metaphyseal density will surely develop. In the early case, however, they are frequently absent and, therefore, a very unreliable sign. Their absence does not rule against the diagnosis and should not prohibit further search for chemical evidence of plumbism.

Confusion with the normally dense metaphyses in children from 18 months to approximately 3 years of age is perhaps the most common cause for a false positive diagnosis of lead poisoning. The normal growth lines are usually not so thick or heavy as the lines produced by lead.

Two of the 17 control roentgenograms were read as borderline by one of the observers. Neither child had any of the signs or symptoms associated with lead poisoning. Both of these roentgenograms were interpreted to be normal by Dr. Caffey. One of the control roentgenograms was read as positive by two observers and normal by Dr. Caffey. This child had poliomyelitis, but because of the history and laboratory findings consistent with plumbism, should have further work-up.

Less frequent causes of dense transverse bands are bismuth deposits,[3] changes produced by aminopterin administration,[8,18] healing rickets,[19] vitamin A deficiency,[6] and metallic phosphorus.[7,15]

The early diagnosis of lead poisoning is imperative if we are to prevent permanent neurologic damage. A history of pica should alert the physician of the possible ingestion of lead. The usual laboratory determinations should be done and the diagnosis confirmed by the demonstration of excessive urinary excretion of lead following a test dose of versenate.

SUMMARY

Transverse bands of increased metaphyseal density ("lead lines") are often absent in children with early lead poisoning. Conversely, young children may have dense metaphyses normally. For these reasons, roentgenographic findings should be given secondary consideration when diagnosing lead poisoning. The absence of lead lines in the long bones should not discourage further search for chemical evidence of plumbism.

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We are grateful to Doctor John Caffey for his interest in this project and for the time spent in interpreting these roentgenograms.

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METAPHYSEAL DYSOSTOSIS*

REPORT OF FIVE FAMILIAL AND TWO SPORADIC CASES OF A MILD TYPE

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THE clinical and roentgenographic findings of most of the different skeletal dysplasias resemble one another to some degree, and exact clinical and roentgenographic classifications are impossible in some cases. The existence of mixed, intermediate, and abortive forms causes additional diagnostic difficulties. Furthermore, there are some intrinsic skeletal diseases which resemble one another so closely that clinical differentiation of them is unsatisfactory even after detailed study.

For these reasons, the roentgenographic identification of mild changes characteristic of metaphyseal dysostosis in healthy appearing patients of small stature is important and useful because, at present, there are no other means of recognizing them. In severe cases, the roentgenographic diagnosis is conclusive, but when the changes are slight the diagnosis often remains uncertain.

Weil[9] recognized two clinical types of metaphyseal dysostosis; the mild Schmidt type[7] and the severe Jansen type;[4] however, in some patients, the irregular uneven changes in different bones in the same individual suggest a mixed type.[5,8] Catal[2] points out that occasionally even the metaphyseal and the epiphyseal types of dysostosis overlap.

In this paper, 6 children and 1 adolescent are described. All were short—below the 2 standard deviation normal range in height and weight (Fig. 1) and all had normal biochemical tests. We believe that these patients are examples of the mild form of metaphyseal dysostosis because of the deficiencies in mineralization of the shafts at the metaphyses.

REPORT OF CASES

Case 1. B.A., a boy, 12 years and 10 months of age, was admitted to the Pediatric Clinic on December 15, 1961, because of his short stature (Fig. 2). He was the second child of healthy young parents. Gestation and delivery were uncomplicated and he appeared to be normal at birth. Growth and development were thought to be normal during the first several years of life; however, when the child was 6 years of age, he was conspicuously shorter than other children of his age and this difference in stature continued to increase. During the last few years, when he was 9 to 12 years of age, "he stopped growing altogether." Otherwise he had always been healthy. The father was of normal height. The mother, who died some years before, was said to have been short but her exact height was unknown. Two sisters of the mother were also said to be short, but healthy. The exact height and weight of Case 1 at the time of admission are given in Table I, and are compared with the normal in Figure 1. His laboratory findings are given in Table II. On physical examination, some shortening of the limbs was found. Roentgenograms of the hands were taken to determine his bone age and the metaphyseal disturbances in the distal ends of the radius and ulna were first noted (Fig. 3*A*). Roentgenograms of the entire skeleton showed normal development of all the epiphyseal ossification centers. In the metaphysis of the long bones, however, the clear cartilage zones were deepened and the ends of the shafts were irregular. These changes were most pronounced at the distal femoral metaphyses and the proximal tibial metaphyses (Fig. 3*B*). The lumbar and lower thoracic vertebral bodies were slightly flattened with some marginal irregularities, which we considered at this age normal mineralization of the vertebral rings. The frontal bone bulged slightly outward and there was questionable orbital hypertelorism. The

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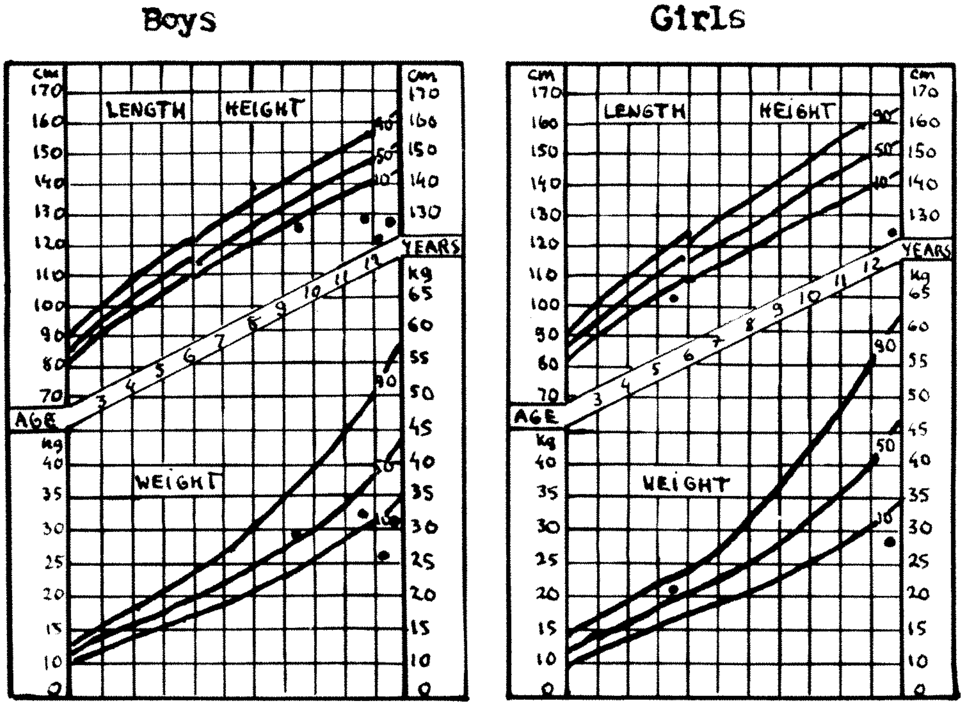

Fig. 1. Graphs of median height and weight for 4 boys and 2 girls—2 standard deviation range (according to Stuart and Stevenson). The heights of all 6 patients were well below the lower limits of the 2 standard deviation normal range.

bone age in the hands was normal according to the standards of Pyle and Greulich. No other diagnostic changes were found in the skeleton. In our opinion, the incomplete mineralization of the ends of the shafts warranted the diagnosis of mild metaphyseal dysostosis.

Case 2–5. Because of this diagnosis, the father and 4 siblings of Case 1 were examined. The age, height, and weight of these siblings (Case 2, 3, 4 and 5) are shown in Table I and with the exception of Case 2, who was omitted because of his older age, are compared with the normal in Figure 1. The laboratory findings for the 4 siblings are given in Table II. Physical examinations revealed in all of the siblings, as in Case 1, a slight shortening of the limbs

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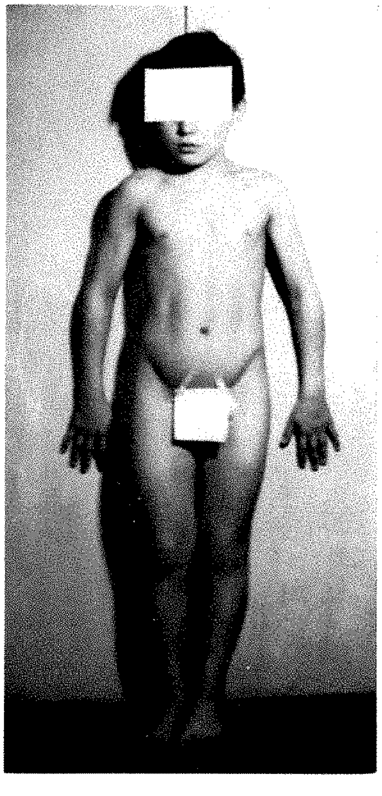

Fig. 2. Case 1. Boy, aged 12 years, 10 months. Photograph of patient showing that although short for his age, he has no gross deformities. The muscular development is excellent.

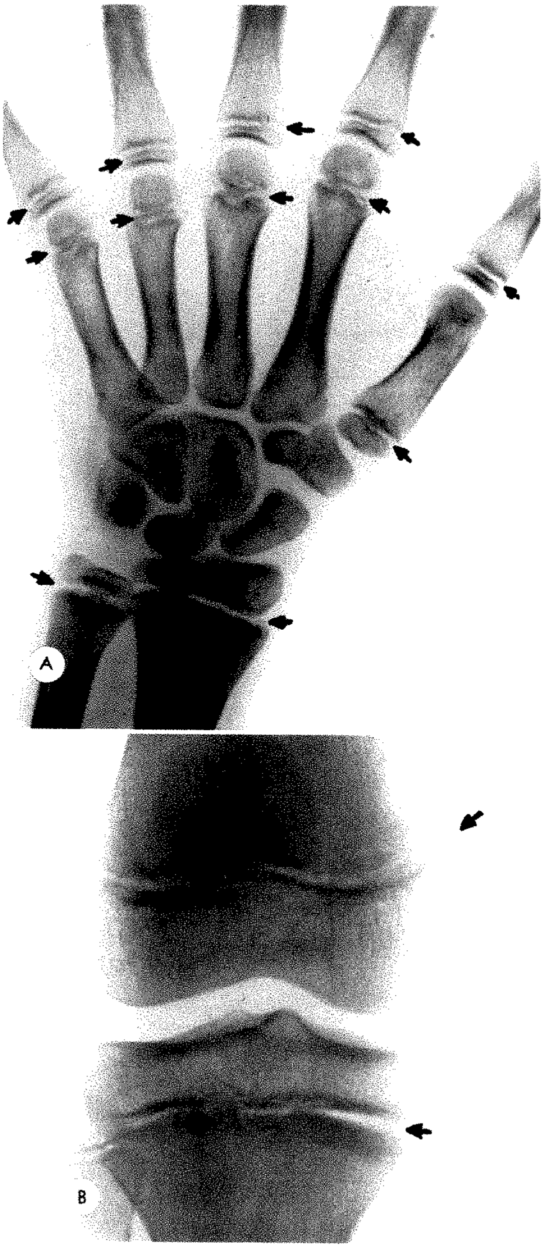

Fig. 3. Case 1. (*A*) Right hand and (*B*) knee at 12 years, 10 months of age, show deepened transverse clear zones between the ends of the shafts and the epiphyseal ossification centers. The deepening is due to inadequate mineralization at the end of the shaft; the ossification centers are normally mineralized. The changes are most marked in the radius and ulna, but are also clearly seen in the metacarpals and phalanges when compared with an average normal hand (Gruelich and Pyle). The edges of the shafts are irregular but the shaftward edges of the ossification centers are smooth. Changes of this kind are found in juvenile rickets, juvenile hypophosphatasia and juvenile metaphyseal dysostosis of the mild type; the normal biochemical findings in this patient exclude the first two diseases. At the knees the clear zones between the shafts of the femur and tibia and their epiphyseal ossification centers are deepened and have the same significance as the lesions in the hands. Arrows point to the deepened clear zones and the irregular edges of the shafts. Similar findings were present in this patient's siblings (Cases 3, 4, and 5 whose ages were 11, 9, and 5 years, respectively).

with possible bulging of the forehead and questionable orbital hypertelorism. The physical findings in the father were normal. The roentgenologic findings in all siblings were similar to those of Case 1. A satisfactory appraisal of the metaphyses in the 16 year old brother (Case 2) was impossible because the epiphyseal ossification centers had already fused with their shafts. In Cases 3 and 4 the changes were most obvious in the distal ends of the ulnae, radii and femora, as well as in the proximal end of the tibial shafts as in Case 1. In Case 5, however, no diagnostic changes in the distal radial and ulnar metaphyses were found, but there were distinctly abnormal changes in the proximal tibial and distal femoral metaphyses. The diagnosis of metaphyseal dysostosis of mild type seemed warranted for all of these siblings.

Case 6. S.P., a boy, 11 years and 10 months of age, was admitted to the Pediatric Clinic be-

Table I

Case No.	Age	Height (cm.)	Weight (kg.)
1	12 yr., 10 mo.	127	31.000
2	16 yr.	158	60.100
3	11 yr., 8 mo.	129	32.250
4	9 yr., 6 mo.	127.5	29.500
5	5 yr., 6 mo.	103	20.100
6	11 yr., 10 mo.	120	26.000
7	11 yr., 9 mo.	124	28.750

cause of short stature, on October 18, 1962. He was the second child of healthy young parents and his gestation and delivery were uncomplicated. He appeared to be normal at birth and weighed 2,600 gm. His motor development was normal. His speech, however, was retarded; he first began to talk effectively during his fourth year. At about the same time, the mother noticed that he was shorter than other children of his age and this difference increased during the following years. He did well and had no serious illnesses of any kind. The findings on physical examination were all normal. His vocabulary was poor but the general impression of the psychiatrists was that his low I.Q. of 90 resulted from environmental factors. I^{131} uptake was normal. His height, and weight are given in Table I and Figure 1, and his laboratory findings in Table II. On roentgenographic examination, the metaphyseal clear zones were found to be deepened and the edges of the shafts irregularly mineralized. These changes were pronounced at the distal metaphyses of the ulnae, radii, and femora and at the proximal metaphyses of the tibiae. Pneumography of the brain was normal.

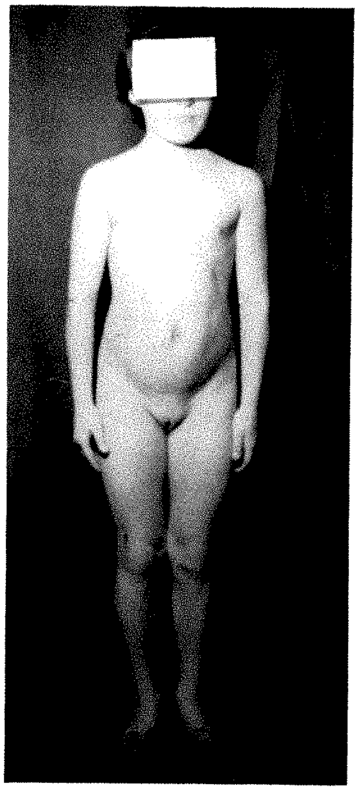

Fig. 4. Case 7. Girl, aged 11 years, 9 months. Photograph of patient showing that there are no abnormalities although she is short. The muscles are well developed.

Case 7. S.W., a girl, 11 years and 9 months of age, was admitted to the Pediatric Clinic because of short stature on October 29, 1962 (Fig. 4). She was the second child of healthy young parents. Her gestation and delivery were uncomplicated and the infant was thought to be normal at birth. However, she was not weighed or measured. Both mental and motor development were normal. When she was 6 years of age, her mother first noticed that she was shorter than other children of her age, and this difference continued to increase. During the last few years it seemed that she had stopped growing. She was always asymptomatic. The height of her mother was 152 cm. and of her brother, 14 years of age, 142 cm. The father was said to be one head taller than the mother. The physical findings were all normal with the exception of shortness of stature. The patient's height and weight, at the time of admission are given in Table I and Figure I and the laboratory findings in Table II. On roentgenographic examination, the metaphyseal clear zones were deepened and the ends of the shafts were irregularly mineralized. These changes were especially noted in the distal metaphyses of the ulnae, radii and femora and in the proximal metaphyses of the tibiae (Fig. 5, *A* and *B*).

Table II

Case No.	Ca (mg. per cent)	P (mg. per cent)	Alkaline Phosphatase (Bodansky units)
1	9.4	3.9	7.6
2			
3	9.4	4.0	7.6
4	9.1	3.9	10.2
5	9.2	4.1	9.4
6	10.4	4.1	7.2
7	9.85	4.0	6.4

Other laboratory studies in Cases 1, 6, and 7 included routine blood and urine examinations, urine chromatography, electrophoresis, glucose tolerance tests, analysis of stomach and duodenal juices, and nonprotein nitrogen determination. Serum urea and stool fat were within normal limits. The roentgenographic gastrointestinal examinations were also normal. In Cases 3, 4, and 5 the laboratory studies included routine blood cell counts, urinalysis, nonprotein nitrogen, serum urea and urine chromatography. All findings were within normal limits.

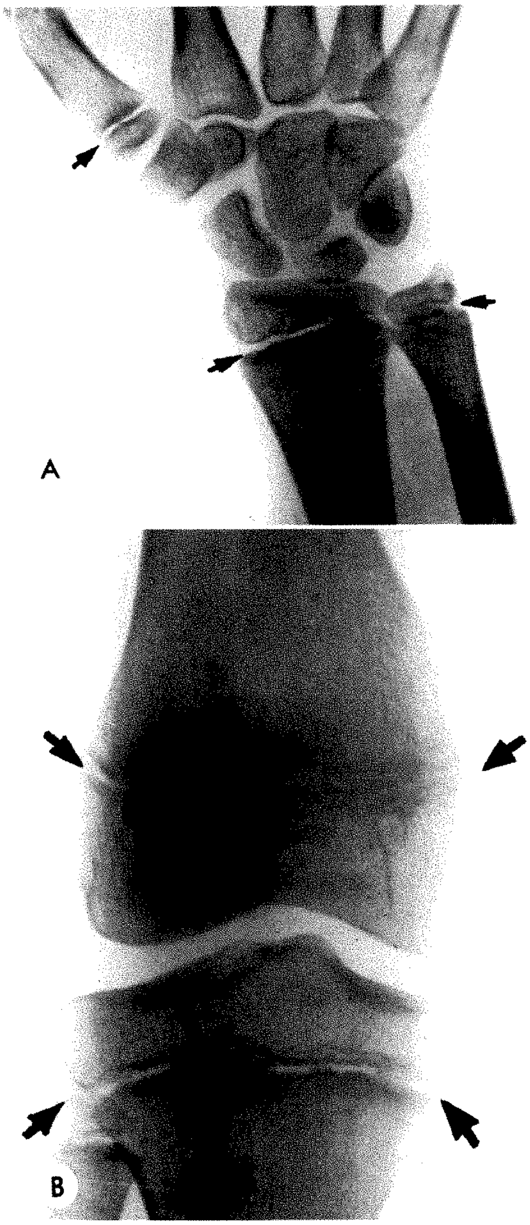

Fig. 5. Case 7. (*A*) Right wrist and (*B*) knee at 11 years and 9 months. The clear, cartilaginous transverse zones between the shafts and the epiphyseal ossification centers are deepened and the metaphyseal edges of the shafts are slightly irregular. As in all of the described cases, the deepening of the cartilage space between the edge of the shaft and the epiphyseal ossification centers is due to inadequate mineralization of the shaft. The ossification centers and the shafts are normally mineralized and their shaftward edges are smooth.

DISCUSSION

The only complaint of all the patients was shortness of stature. In Case 1, the metaphyseal disturbances in the distal ends of the radial and ulnar shafts prompted us to make roentgenograms of his entire skeleton. When the diagnosis of metaphyseal dysostosis appeared evident, his father and all siblings were also examined. All of the children were almost identical morphologic types with shortness of stature due to slight shortening of the extremities. In all the roentgenographic findings in the metaphyses were similar and thus the diagnosis of metaphyseal dysostosis seemed warranted. The changes were most prominent in the distal metaphyses of the radii, ulnae, and femora, and in the proximal metaphyses of the tibiae. It is probable, although not proven, that the 16 year old short brother had had metaphyseal lesions similar to those of his siblings in his early childhood, before the shafts and epiphyseal ossification centers fused. Both roentgenographic and clinical findings were normal in the father. The mother and 2 of her sisters seemed to have been conspicuously short. The shortness of stature and the similarity of the roentgenographic changes in Cases 1, 2, 3, 4 and 5 indicate almost certainly a dominant inheritance of this disease. In Cases 6 and 7, however, no relatives were conspicuously short and these two appeared to be sporadic cases with a recessive type of inheritance, or perhaps inheritance due to mutation. In all instances the children appeared to be of normal length at birth and their shortness was not noticed during the first 3 years of life. The growth deficiency, however, was recognized in the fourth year of life by the mother of 1 case (Case 6); in the other cases the mothers noticed the shortness of stature at about 6 years of age. This shortness was confirmed later in our clinical examinations in all cases. In all cases the main roentgenographic changes were the deepened clear zones between the end of the shafts and their epiphyseal ossification centers which were normal. This deepening of the cartilage space when normal epiphyseal ossification centers are present is certain evidence of inadequate ossification at the end of the shaft. Changes of this kind are found in mild refractory rickets and also in the juvenile mild type of hypophosphatasia. The presence of normal phosphorus content in the sera and the absence of low serum phosphatase activity exclude these two possibilities and imply the diagnosis of metaphyseal dysostosis by exclusion. The exact age of the patients at onset of the roentgenographic changes cannot be determined from our observations because we saw none of the children during the first months or years of life; however, there were no diagnostic changes in the radii and ulnae in Case 5 at 5 years of age, although distinct changes were present in the bones at the knee joint. It seems likely that early in the disease the roentgen examination of the knees would be more informative than the roentgen examination of the hands; however, in older patients, the hands show the unmistakable changes in all of the tubular bones as well as in the radii and ulnae.

McKusick[6] points out that, when studied singly, the small number of individuals of the general population with mild manifestations of disease cannot be considered as abnormal because of resemblance to normal variants. These slight manifestations, however, can be recognized as abnormal when the total genetic and clinical picture of entire families is studied and evaluated.

These statements emphasize the necessity of knowing the height of children before roentgenograms of the hands are interpreted for skeletal age. The radiologist who notices slight bone deficiencies in the metaphyseal regions should be much more careful in evaluating them as abnormal when the height of the child is below the normal range. He can confirm his opinions by comparing his findings with normal standards and by the study of other metaphyses in the patient, and also by making the same studies in other members of the family. By this means more cases of metaphyseal dysostosis would be recognized. Caffey has long stressed the difficulty in differentiating the normal variant in the normal growing skeleton from the findings of early mild disease. We want to emphasize that the changes encountered in our children—deep clear cartilage zones—should be classified as variants with extreme caution. According to Dorland, "variation" is a deviation in the characteristics of an individual from those typical of the group to which he belongs. "Abortive" signifies "cutting short" in the course of a disease, and its termination without complete evolution.[3] It is often impossible to draw a sharp line between normal variants and the abortive forms of metaphyseal dysostosis. The major problem in the classification of all of endochondral dysostoses is illustrated by the difficulties encountered in our mild cases. These difficulties, of course, are due to the great difference in the severity of the disease in different individuals and different families. In all of our cases the metaphyseal disturbances were less marked than those in the intermediate Schmidt type, and there were no gross deformities of the extremities. But the changes, after careful study, could not be classified as normal. When the morphologic, roentgenographic, and genetic data were taken into account, an incomplete form of metaphyseal dysostosis was recognized by the lessened height of all of the siblings and the presence of deepened cartilage zones in all of the siblings in one family. These mild cases seem to fill the gap between the normal and the Schmidt moderate type of metaphyseal dysostosis; and point out the gradation of this disease from our abortive mild form through the moderate Schmidt type on to the most severe Jansen variety. Probably, detailed biochemical, histologic and genetic studies will supply more sensitive diagnostic tests, and, perhaps, even the cause of the metaphyseal dysostosis syndrome. In the meantime, adequate roentgenographic examination and evaluation of children with short stature and without biochemical evidence of other diseases will probably uncover more families with findings similar to those of our patients.

SUMMARY

Seven cases of shortness of stature with metaphyseal irregularities and deficiencies in mineralization are reported. Six were children ranging in age from 5 to 12 years and 1 was an adolescent, 16 years of age. Four of the children were siblings of the adolescent. A diagnosis of the abortive form of metaphyseal dysostosis was made in these cases because of the changes in the ends of the shafts at the metaphyses and the absence of biochemical findings indicative of refractory rickets or hypophosphatasia. The importance of shortness of stature in pointing to a mild degree of metaphyseal dysostosis is emphasized.

Because of the great variation in the roentgenographic findings in patients with the different types of metaphyseal dysostosis, its classification is difficult and would be greatly enhanced if various degrees of metaphyseal dysostosis could be found in single families.

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FAMILIAL OSTEOECTASIA WITH MACROCRANIUM*

By HARRY BAKWIN, ARCHIE GOLDEN *and* SHELDON FOX

IN 1956, Bakwin and Eiger[1] described a Puerto Rican girl, 7½ years old, with bowing and generalized osteoporosis of the long bones, multiple fractures and macrocranium. The clinical and roentgenologic findings did not fit into any recognized syndrome. A diagnosis of osteogenesis imperfecta was considered, but it was rejected because of two features which were considered incompatible. The medullary cavities in the unfractured bones were expanded instead of being narrowed and the bones of the skull were greatly thickened.

The history, briefly, was one of repeated fractures, beginning before the end of the first year of life. Subsequently, fractures of the long bones of the upper and lower extremities occurred at the rate of about 2 each year. Bowing of the extremities and enlargement of the head were noticed at about 3 years of age. At 7½ years the serum calcium varied from 9.1 to 11.2 mg. per 100 cc. at different times, the serum inorganic phosphorus varied from 3.1 to 6.0 mg. per 100 cc. and the serum alkaline phosphatase activity fluctuated between 5.9 and 23.7 Bodansky units. On two occasions the ester cholesterol was reduced, later it was normal.[1]

Since 1956 this patient, referred to as Case 1 in the present paper, has been in Bellevue Hospital repeatedly with fractures and increasing incapacity. In 1956 and 1957 multiple osteotomies and intramedullary nailings of the right femur and tibia and the left tibia were performed in an attempt to straighten the lower extremities. In 1959, because of pain and great swelling, the right femur was incised and a large cyst containing brown fluid was found. A diagnosis of aneurysmal bone cyst was made. She was in an automobile accident in 1960 and sustained fractures of the left humerus, left femur and right tibia. These healed well.

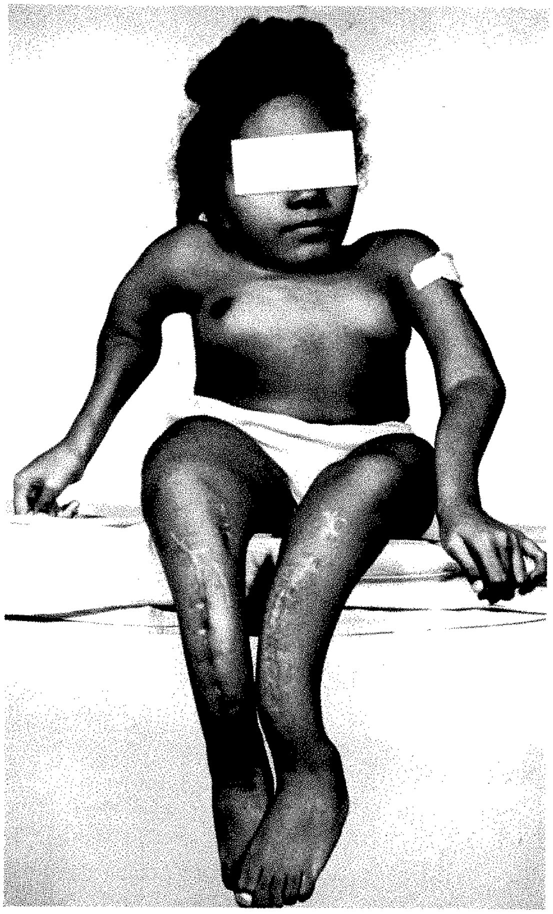

Fig. 1. Case 1 in 1962. Aged 14 years. The head is large, the forehead high: There are generalized deformities, in part due to the primary bone disease, in part to fractures.

The head has continued to grow. The head circumference has increased from 60 to 65 cm. and the thickness of the skull in the parietal region from 2.5 cm. in 1956 to 4.2 cm. in 1962. At present she is 14 years old (Fig. 1), incapacitated and confined to a wheel chair. Her skull roentgenogram is shown in Figure 2.

Examination of the fundi by Dr. A. M. Denby revealed early macular degeneration, grossly constricted visual fields with a relative central scotoma in both eyes and, in

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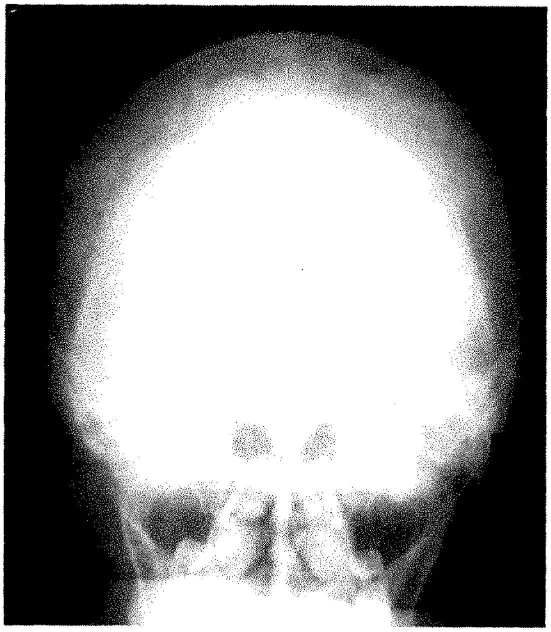

FIG. 2. Case I in 1962. Roentgenogram showing the greatly widened skull.

the electroretinogram, grossly diminished scotopic and photopic potentials.

Recent laboratory data are included in Table I. Leukocyte alkaline phosphatase examinations by Dr. Donald Briggs over a period of 2 weeks gave values of 179, 230 and 145 (normal values 20 to 80). Increased leukocytic phosphatase activity is present in association with chronic infections, mongolism, polycythemia, acute leukemia and a number of other pathologic states.

Recently, a younger sister of the patient and the only sibling (Case II) was admitted to Bellevue Hospital at the age of 11 years because of weakness and fatigability.

REPORT OF A CASE

CASE II. Conchita R. was born in Puerto Rico. She grew and developed normally until 2 years of age when bowing of the lower extremities was noticed. At 3 years she fell and broke her right femur. This healed well but the bowing progressed in the lower limbs and developed in the upper limbs as well during the next few years. At 7 years of age she fell and broke the right humerus. Healing was prompt.

The deformities increased during the past 4 years. Her height was about average for her age and, despite her deformities, she walked well. She is normal mentally and has progressed well in school. Three to four weeks prior to ad-

TABLE I

LABORATORY DATA

	Case I*	Case II
Blood		
Hemoglobin (gm. per cent)	11.0	4–10.5
Hemoglobin electrophoresis	Adult hemoglobin	Adult hemoglobin
Sickle cell preparation	Negative	Negative
White blood cells	7,200	9,250
polymorphonuclears	40%	66%
lymphocytes	48%	34%
monocytes	8%	0
eosinophils	2%	0
Serum		
Calcium (mg. per cent)	8.5–10	8.3–9.2
Inorganic phosphorus (mg. per cent)	3.0–6.5	5.5–6.5
Alkaline phosphatase activity (Bodansky units)	20–22	20–24
Acid phosphatase activity (Bodansky units)	0.1	0.3
Sodium (mEq./L.)	142	139
Potassium (mEq./L.)	4.4	4.5
Chloride (mEq./L.)	103	103
CO_2 content (mEq./L.)	24	23
Iron content (μg. per cent)	130	50
Iron binding capacity (μg. per cent)	330	363
Protein electrophoresis	Normal	Normal
Protein (gm. per cent)		
total	7.3	7.1
albumen	3.7	3.9
globulin	3.6	3.2
Urea nitrogen (mg. per cent)	10	10
Thymol turbidity (units)	5	2
Glutamic oxaloacetic transaminase (Karmen units)	18	49
Cholesterol (mg. per cent)	165	173
VDRL	Negative	Negative
Bone marrow smear	Normal	Normal
Chromosome pattern	Normal	Normal
Urine		
pH	6.0	6.0
Specific gravity	1.007–1.033	1.010–1.023
Albumen	Absent	Absent
Sugar	Absent	Absent
Sediment	Negative	Negative
Aminoacid pattern	Normal	Normal
Sulkowitch test	1+	1+
phosphorus output (mg. per 24 hr.)	325	640
creatinine clearance (ml. per min.)	92	95
Stool	Negative	Hookworm

* Values obtained in 1962.

mission she became easily fatigued and weak. She then was brought to New York City by her mother. She had been treated for intestinal parasites in Puerto Rico. There was no history of melena or bleeding elsewhere. Menses had not begun.

The skin and mucous membranes were pale. Her head was large with a broad forehead. The face was wide, the nose flat and broad and there was moderate orbital hypertelorism (Fig. 3). The neck was normal. The chest was symmetric but short. The liver was palpable 2 cm. below the right costal margin. The spleen and kidneys were not felt. The external genitalia were normal. There was mild dorsal kyphosis and lumbar lordosis and a slight C-shaped dorsolumbar scoliosis convex to the left.

All the long bones were widened. Cubitus valgus with 20 degree flexion contractures was present at both elbows. The right humerus was bowed anteriorly. Genu valgum was present with moderate anterolateral bowing of both femurs which were widened in the anteroposterior diameters. Both lower legs were bowed anteriorly with large anteroposterior diameters suggestive of sabre shins. The fourth toes were short.

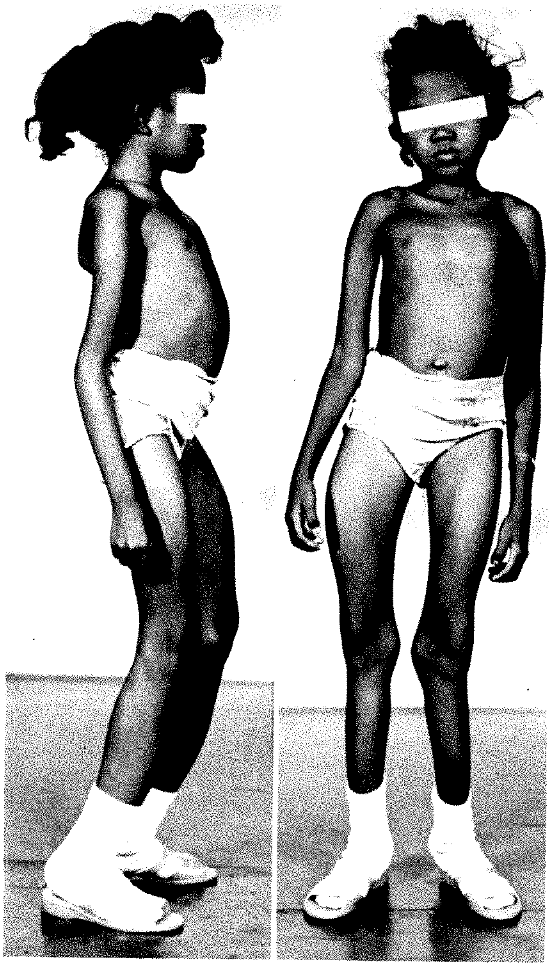
Fig. 3. Case II. Aged 11 years. The head is large, the forehead high, the face wide. Crouching stance. Bowing of the lower extremities and the right humerus.

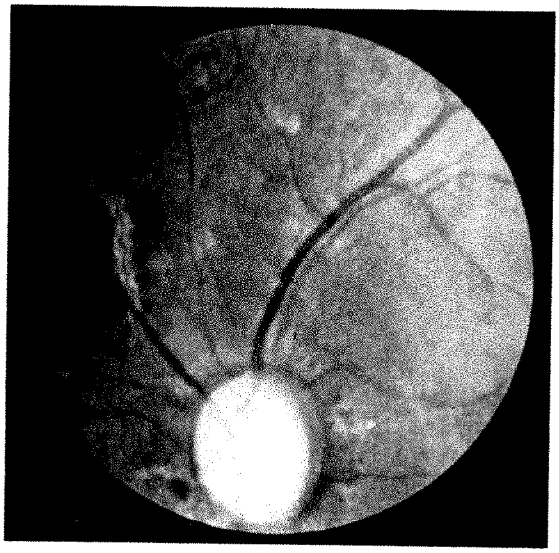
Fig. 4. Case II. Left fundus. The large angioid streak on the nasal side of the disk above and a smaller angioid streak below, as well as the hyaline refractile body and three more hyaline bodies temporal to the disk are seen.

The blood pressure was normal.

Audiometry showed a mild, mixed hearing loss on the right and moderate mixed hearing loss on the left.

Four teeth had cavities. Roentgenograms showed lace-like trabeculation of the mandible and maxilla and intact lamina duras. Skin biopsy was normal.

The scleras were white. Muscular balance was normal. Visual acuity was 15/15 on the left and 15/70 on the right. The visual fields were normal as was color vision. Fundoscopic examination revealed on the nasal side of the right disk an angioid streak, appearing as a white choroidal defect with thin, irregular black pigment. Two similar angioid streaks were seen in the left fundus. In addition, in the left eye just temporal to the left disk, a single hyaline refractile body and just temporal to the macula 3 more hyaline bodies were seen (Fig. 4). An electroretinogram demonstrated slightly diminished scotopic and photopic potentials which may be within the lower limits of the normal range.

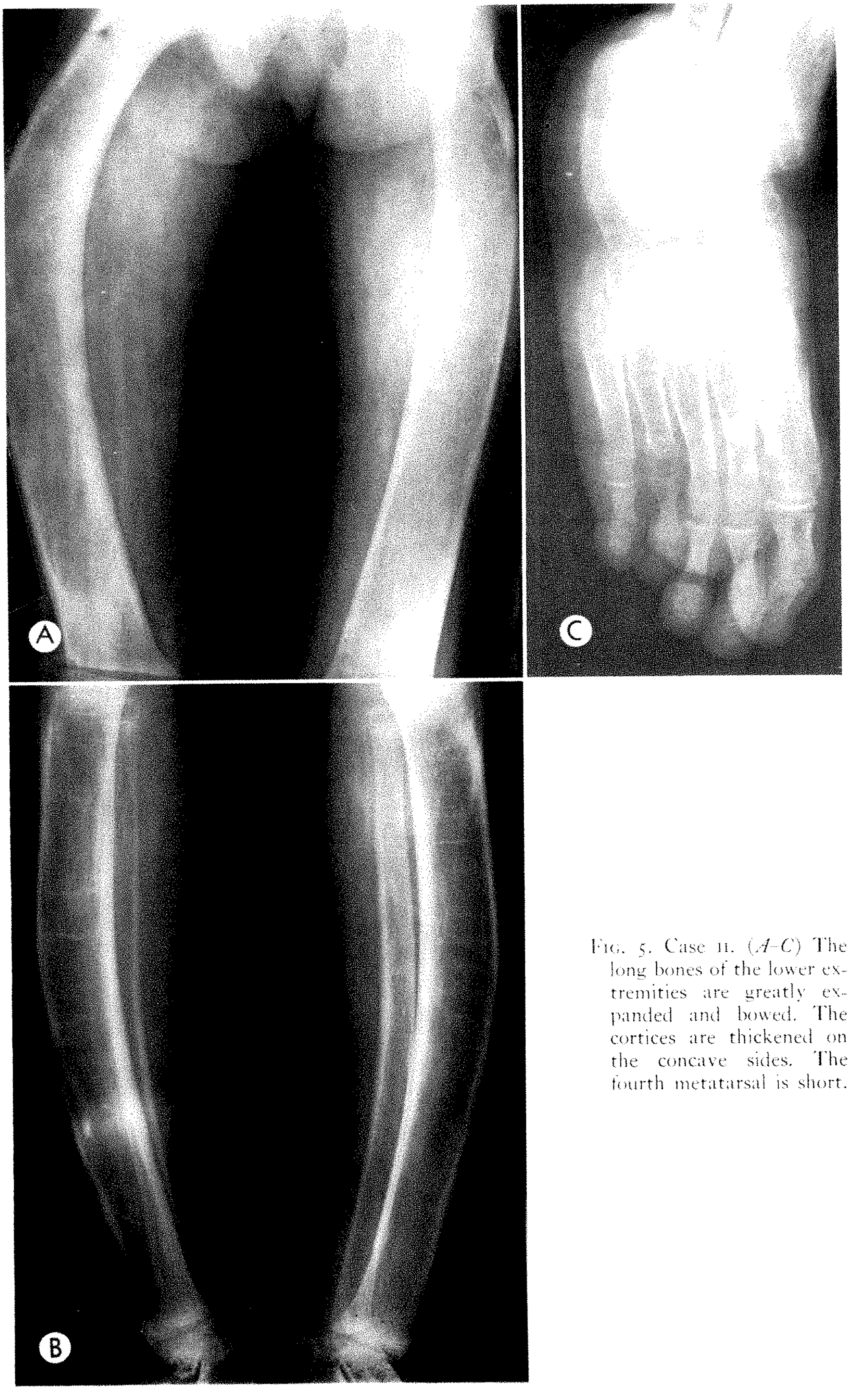

FIG. 5. Case II. (*A–C*) The long bones of the lower extremities are greatly expanded and bowed. The cortices are thickened on the concave sides. The fourth metatarsal is short.

LABORATORY DATA

The laboratory data on the 2 sisters are shown in Table 1. The serum calcium was slightly reduced, varying from 8.5 to 10 mg. per 100 cc. in the older sister and 8.3 to 9.2 in the younger sister. The serum phosphorus was usually high. The serum alkaline phosphatase activity was also moderately elevated, from 20 to 24 Bodansky units. Following a fracture of the clavicle, the serum phosphatase in Case II rose to 44.6 Bodansky units.

On admission Case II showed a hemoglobin of 4 gm. per 100 cc. The stools contained hookworm. The hemoglobin rose to 10.5 gm. following treatment for the hookworm and the iron deficiency. Other blood constituents were normal.

In Case II following the injection of 200 units of parathyroid extract, the phosphorus reabsorption decreased by 13 per cent. A similar result was obtained in Case I. These decreases are in the normal range. Case II showed a normal leukocyte alkaline phosphatase activity on 3 occasions (values (67, 54, 78).

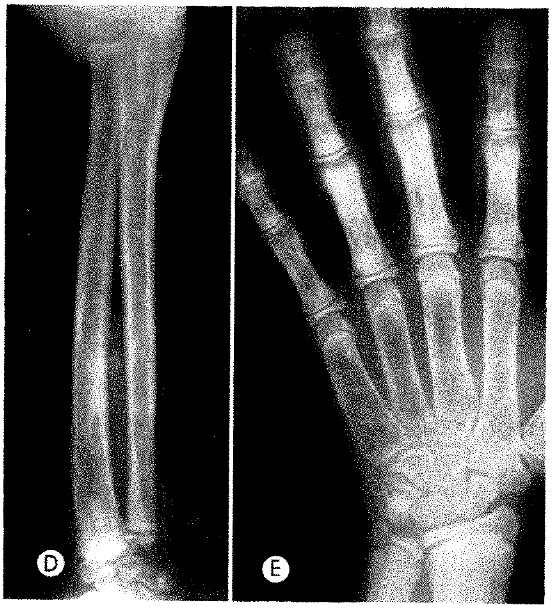

Fig. 5. (*D* and *E*) The bones of the upper extremity are expanded, the cortices slightly thickened. The bones of the hand are expanded. All the bones are osteoporotic and show coarse markings.

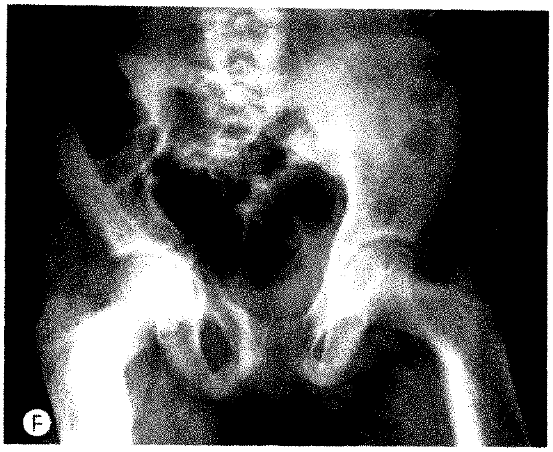

Fig. 5. (*F*) The pelvis is constricted, the outlet asymmetric and the iliac bones flared.

ROENTGEN FINDING IN CASE II
(Fig. 5, *A–G*)

The long bones of the lower extremities were greatly expanded, bowed, and osteoporotic. The cortices on the concave sides were thickened. The bony texture was

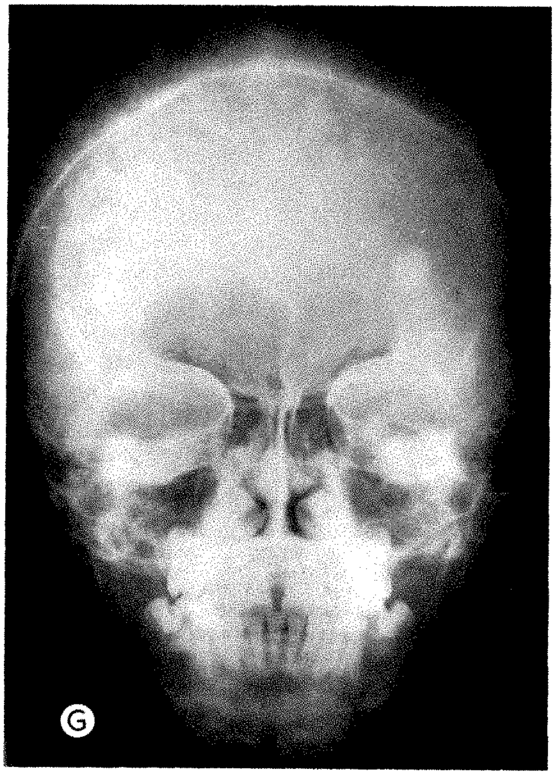

Fig. 5. (*G*) The bones of the skull are greatly widened and show a patch of increased density.

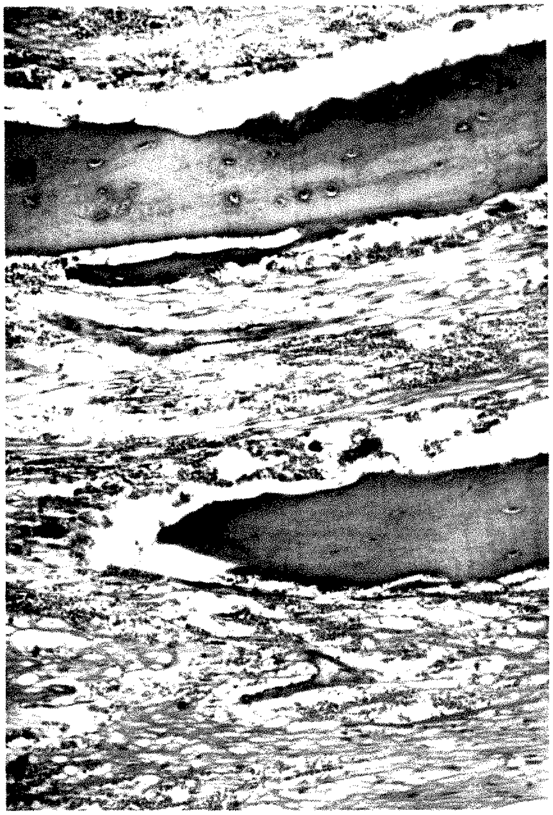

FIG. 6. Case II. Microscopic appearance of bone. The marrow spaces are filled with vascular fibrous tissue. There is a moderate amount of osteoclastic and osteoblastic activity.

coarse with numerous transverse lines. The bones of the upper extremities were also expanded and osteoporotic, the cortices slightly thickened. The right humerus was slightly angulated at the site of an old fracture. The bones of the hands were expanded and osteoporotic with coarse trabeculations. The fourth metatarsal bones were short.

The bones of the calvarium were greatly thickened, measuring 2.5 cm. in the parietal region. A round patch of increased density, about 1 cm. in diameter, was visible in the left frontal region.

The pelvis was constricted in its transverse diameter, which produced mild intrapelvic protrusion of the acetabulums and narrowing of the obturator foramen. The iliac bones were flared. The ribs and spine were normal.

Bone biopsy, reported by Dr. Henry L. Jaffe, showed that the cortex was lamellated and practically all of the osseous tissue was of the nature of primitive, coarsely-fibered bone. In the spaces between the osseous tissue there was highly vascularized loose connective tissue. Osteoclasts were seen but were not excessive. Osteoblasts were also present (Fig. 6). Dr. Jaffe stated "My impression is of profoundly porotic cortical bone. If this is osteogenesis imperfecta it is very atypical. The section in no way resembles Paget's disease."

FAMILY HISTORY

The parents were first cousins. There was no family history of blue scleras, fragile bones or deafness. The parents' eye-grounds were normal.

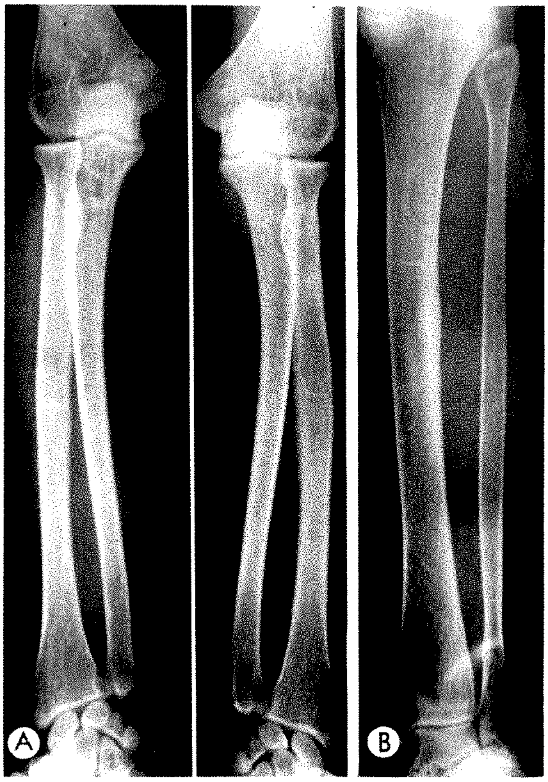

FIG. 7. (*A* and *B*) Roentgenograms of the mother showing similar bone changes. There is expansion of the left radius, left tibia and left fibula, and thickening of the cortex on the inner side of the left tibia.

Roentgenograms of the father's bones showed only shortening of the fifth right metacarpal.

The mother was of average height without clinical deformities. The head was large, the hair-line low and the face very wide. Roentgenograms of her bones revealed changes similar to those in the patients but less marked (Fig., 7 *A–D*). The skull bones were moderately thickened. There was one round, indefinitely outlined patch of increased density, 1.2 cm. in diameter, in the parietal region and two similar patches in the frontal region. The left radius and left fibula were slightly wider than the right. The left tibia was considerably expanded. The cortex was thickened just above the middle of the left tibia on the outer aspect. The right fifth metacarpal was short, measuring 4.0 cm. as compared with the left which measured 4.7 cm. The fourth metacarpal was also slightly shorter on the right. No changes were seen in the feet.

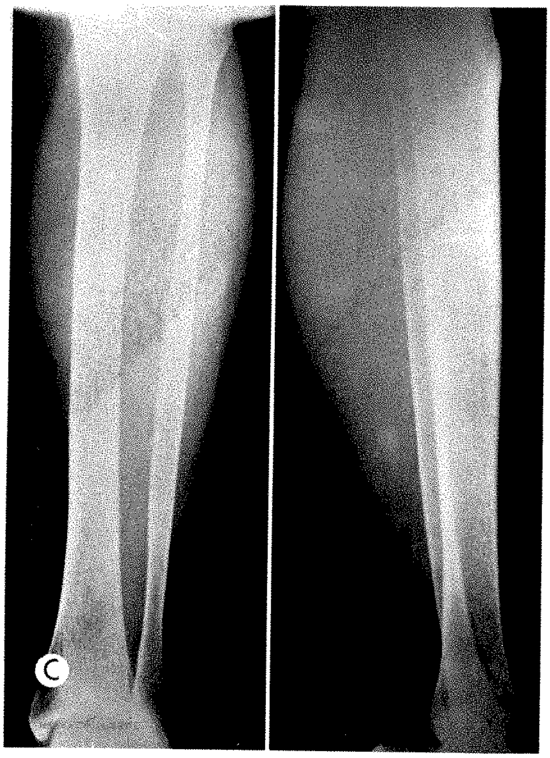

Fig. 7. (*C*) Roentgenograms of the mother's right tibia and fibula show very little change.

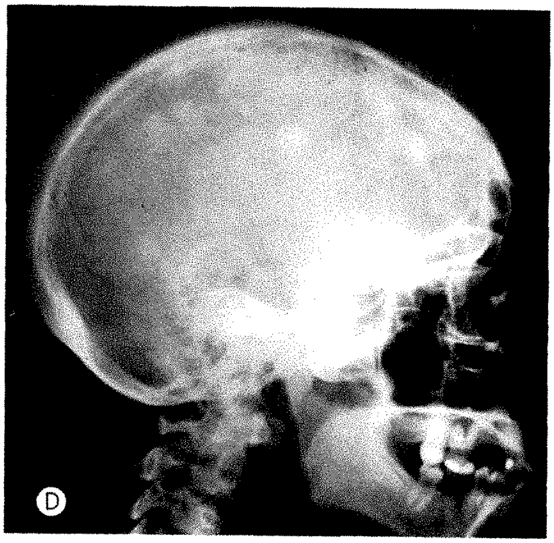

Fig. 7. (*D*) There is slight thickening of the mother's skull and there are areas of increased density in the skull bones.

Serum calcium, inorganic phosphorus, alkaline and acid phosphatase in both parents were normal.

DISCUSSION

Two sisters with generalized bone deformities are described. The medullary cavities of the long bones were greatly expanded and the cortices were thickened and osteoporotic. The bones of the lower extremity were bowed outward and forward. The skull bones were greatly thickened.

The serum alkaline phosphatase activity was regularly and moderately elevated in the younger sister; the older sister, however, had a normal value in one examination. The serum alkaline phosphatase activity was normal in the parents.

Both sisters showed degenerative changes in the retina: macular degeneration in the older sister, probably the forerunner of retinitis pigmentosa; and angioid streaks and hyaline bodies in the younger sister, which may be the forerunners of retinitis punctata albescens. Angioid streaks have been described in association with pseudoxanthoma elasticum, Paget's disease, sickle cell disease, primary elastic tissue degeneration and certain macular degenerations.

The mother showed the following bone changes: expansion of the left tibia with cortical thickening, expansion of the left radius and left fibula; wide skull bones with localized areas of increased density and a short right fifth metacarpal. The father showed only shortening of the right fifth metacarpal.

Since the report by Bakwin and Eiger in 1956, 8 similar cases have been recorded in the literature.[2–5] The present Case II makes the tenth case.

Choremis *et al.*[3] described a boy, 11 years old, who had changes in the long bones and skull similar to those observed in our patients. A bone biopsy showed marked acceleration of the two processes, resorption and formation of bone with abundant osteoclasts in the areas of absorption which was interpreted as typical of Paget's disease.

Swoboda[5] described 2 sisters with a severe, generalized, symmetric osteopathy associated with marked tenderness of the extremities. The shafts of the long bones were greatly widened, bowed, and osteoporotic. The cortices were thickened. In addition, the skull bones were thickened with isolated patches of osteosclerosis. The serum alkaline phosphatase activity was markedly elevated in one child (130 King-Armstrong units), in the other it was normal (5.7 Bodansky units). In the bone biopsy the distinctive feature was the cortical new bone formation. This was made up of narrow trabeculae which were normally calcified in the centers or showed as small islands. Between these, and in the deeper portions, there was some resorption of the bony plates. There was also extraordinarily rich connective tissue with variable cell and fiber content but with numerous thin-walled vessels. Numerous osteoblasts were present on the surfaces of the trabeculae. The osteoclasts were not increased. The bone marrow was not remarkable; it was reduced in amount.

Under the heading of "chronic idiopathic hyperphosphatasia" Caffey[2] assembled a group of cases with roentgenologic changes closely resembling those observed in our patients and added 4 of his own. The distinctive features were the expanded and bowed long bones with thickened cortices and the widened skull bones. Muscle weakness was present which sometimes delayed the onset of walking, and later limited activities such as walking, running and jumping. In severe cases all the tubular bones, including the ribs and the hands and feet, showed thickened cortices. The heavy cortex sometimes encroached on the medullary cavities with narrowing and, in some instances, obliteration.

On microscopic examination of the bone, the thick cortex was found to be made up of thin, primitive trabeculae which showed active bone resorption as well as bone production. The intertrabecular spaces were filled with vascular connective tissue. The haversian system was almost obliterated. Contiguous cancellous bone was sharply reduced in amount. The microscopic picture excluded Paget's disease, when criteria applicable to adult cases were used.

SUMMARY

A syndrome has been described with the following characteristics: The disease begins early in life possibly during the first year in some cases. The condition is familial. The most prominent clinical deformities are the large head and the expanded and bowed lower extremities. Motor disability is present to a greater or lesser degree. Intelligence is unaffected and the internal organs are normal. The alkaline serum phosphatase activity is usually elevated. The serum calcium is often slightly reduced but values below 8.0 mg. per 100 cc. have not been observed. Fractures, shortening of some of the finger and toe digits, fever, pain and tenderness have been observed in some patients.

Roentgenograms show greatly expanded long bones, usually including the hands and often the feet, and osteoporosis with coarse trabeculation. The bones of the lower extremities are bowed. The cortices are thick-

ened, most strikingly on the concave aspects of the bowed bones in the lower extremities.

The bones of the skull are markedly thickened. Islands of increased density may also be present.

Microscopic examination shows numerous thin trabeculae and active bone resorption and new bone formation. The intertrabecular spaces are filled with vascular connective tissue.

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We wish to thank Dr. John Caffey for his invaluable assistance.

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THE TRISOMY 18 SYNDROME*

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RECENT improved techniques of chromosome investigation have permitted a more accurate classification of several previously described syndromes of radiologic interest. Knowledge of the basic chromosomal aberrations associated with gonadal dysgenesis, Klinefelter's syndrome, and Down's syndrome (mongolism) has aided in clarifying these diseases and has greatly improved the possibility of accurate prognosis and genetic counseling.

The newer techniques, which allow more detailed examination and classification of the individual chromosomes, have also revealed previously unnoticed findings of importance in clinical pediatrics. On retrospective analysis, the physical features were remarkably similar in those children in whom an extra chromosome in a specific group was observed. One genetic anomaly involves the presence of 7 instead of the normal 6 autosomal chromosomes in the E or 16–18 subgroup. This abnormality has been referred to as the No. 18 trisomy syndrome,[18] trisomy 17–18 syndrome,[23] trisomy 16–18,[24] or E syndrome.[2] The present report comprises a brief review of the application of these new techniques, and an analysis of the roentgen findings in a case of trisomy 18 syndrome and in previously reported cases.

TRISOMY 18 SYNDROME

Smith *et al.*[18] have described the salient clinical features of this syndrome. They observed mental retardation, moderate muscular hypertonicity, failure to thrive, low-set or deformed ears, small mandible, flexion of the fingers with overriding of one finger on another, and foot deformities. The contrast between the common signs and some of the less frequent features of this disease are shown in Table I.

The pathologic features in this syndrome vary somewhat, but some aspects are strikingly consistent. Of 18 patients on whom necropsy results are available, ventricular septal defect, averaging 8 mm. in diameter was found in 17. Patent ductus arteriosus was seen in 8. Diverticulum of the ileum was also common, being present in 8 patients; the site averaged 42 cm. proximal to the ileocecal valve. Anomalies

TABLE I

PHYSICAL ABNORMALITIES IN 25 PATIENTS WITH TRISOMY 18 SYNDROME*

Sex:	Females	19	
	Males	6	
Age:	Average age at death	3.7 months	
	Average maternal age	32 years	
	Average paternal age	35 years	
Head:	Small mandible		18
	Prominent occiput		8
	High-arched palate		6
Chest:	Short sternum		11
Extremities:	Flexed fingers		19
	Decreased hip abduction		12
	Foot deformity, rocker-bottom or club foot		9
	Overlapping fingers		8
	Short toes		8

Less common abnormalities included: *Head and Neck:* Narrow frontal area, cleft-palate or hare lip, hypertelorism, short neck. *Thorax:* Abnormal shape or symmetry, pectus excavatum, widely spaced nipples, prominent vertebral spines, scoliosis. *Upper Extremity:* Increased shoulder mobility, short fingers, angulation of fingers or hands, supernumerary digits. *Lower Extremity:* Small pelvis, prominent femoral necks, flat arch, metatarsophalangeal dislocation, partial cutaneous syndactyly, dorsiflexed great toes.

* Includes the present case and those reported by Brodie and Dallaire,[2] Crawfurd,[4] Edwards *et al.*,[5] Gagnon *et al.*,[6] German *et al.*,[7] Smith *et al.*,[16,18] Steinberg and Jackson,[19] Townes *et al.*,[23,24] Uchida *et al.*[25,26]

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of the urinary tract included ureteral duplication, renal cortical malformation and horseshoe kidney. Membranous defects in the diaphragms were also found in some. A defect in the anterior cerebral falx was occasionally seen, but usually the brain was normal. Many other deformities were seen with less frequency (Table II).

The abnormalities described are usually noted at birth. Failure to thrive and a general downhill course had been noted in all previous cases, with an average survival time of only 3.7 months. Of the 24 patients reported previously, 18 were females. Essential to the diagnosis of this disease is the identification of an extra chromosome in the 16–18 group. The following report describes the twenty-fifth patient reported to date and the oldest survivor known.

TABLE II

FREQUENT PATHOLOGIC OBSERVATIONS AT NECROPSY IN 18 PATIENTS WITH TRISOMY 18 SYNDROME

Ventricular septal defect (average 8 mm. diameter)	17
Patent ductus arteriosus (2 to 12 mm. diameter)	8
Ileal diverticulum (average 42 cm. proximal to ileocecal valve)	8
Double ureters	7
Diaphragmatic defects, muscular or membranous	5
Accessory pancreas	5
Horseshoe kidney or malrotation	4
Short sternum with abnormal segmentation	4
Bicuspid pulmonic valve	4

Less frequent findings included: ***Skull and brain:*** Wormian bones, abnormal cerebral or cerebellar gyri, defective falx anteriorly. *Lungs:* Malsegmentation. *Gastrointestinal:* Ectopic gastric mucosa, cardioesophageal stenosis, pyloric hypertrophy, pancreatic fibrosis, hypoplastic gallbladder and common bile duct, accessory spleen, small or large bowel malrotation. *Genitourinary:* Cystic renal cortical malformation, crossed ectopia with fusion, ureteral stenosis or atresia, ureterocele, posterior urethral web, deficient ovarian tissue. *Musculoskeletal:* Scoliosis, anomalous costochondral junctions, delayed ossification, syndactyly, absent thenar, rhomboid, or posterior deltoid muscles.

REPORT OF A CASE

This girl was born in 1953 after an uneventful pregnancy, except for a transitory maternal virus infection in the first month. The mother was 32 years old, and the father 36; no blood relation to each other is known. One sibling is normal and there is no history of familial disease.

The infant weighed 5 pounds, 13 ounces at birth. Unassisted breathing was reported to have been delayed but details are not known. Development was slow, and she was not able to sit at the age of 2 years. Anomalies had been noted at birth, and when mental retardation became obvious at 2½ years she was admitted for care to a state hospital.

On examination at that time prominent frontal bosses, high-arched palate, nystagmus, and unequal pupils were noted. Anterior dislocation of the hips and club feet were present, and increased deep tendon reflexes and patellar clonus could be produced. The intelligence quotient was estimated at 20. A systolic murmur was heard, and after several episodes of heart failure, a diagnosis of pulmonary hypertension was made. Her weight remained below the third percentile for her age.

Roentgen examination at the age of 7 years was said to have given evidence of a bone defect in the right clavicle, increased vertebral body height, narrow phalangeal shafts, and an enlarged heart with right ventricular prominence. Bone age was estimated at 1.5 years (chronologic age 7 years).

When chromosome investigation showed her karyotype to be trisomic for 1 of the 16–18 group chromosomes, she was admitted to the University of California Medical Center for study. In addition to the findings previously described, low-set ears were present, somewhat deformed by deficiency of cartilage. Two brown, nonelevated nevi were seen in the skin of the lower chest. The nipples were widely spaced (Fig. 1).

A left precordial bulge was present, associated with enlargement of the heart to the left. A Grade III diastolic murmur was heard along the left sternal border at the second intercostal space. A 1 cm. defect of the umbilical abdominal wall, without herniation, was palpable. All muscles were soft and small, and the joints were lax, allowing free passive motion without normal tone or resistance. The fingers, terminally clubbed and slightly cyanotic, were held in flexion and ulnar deviation but could be easily extended by the examiner. The second and third

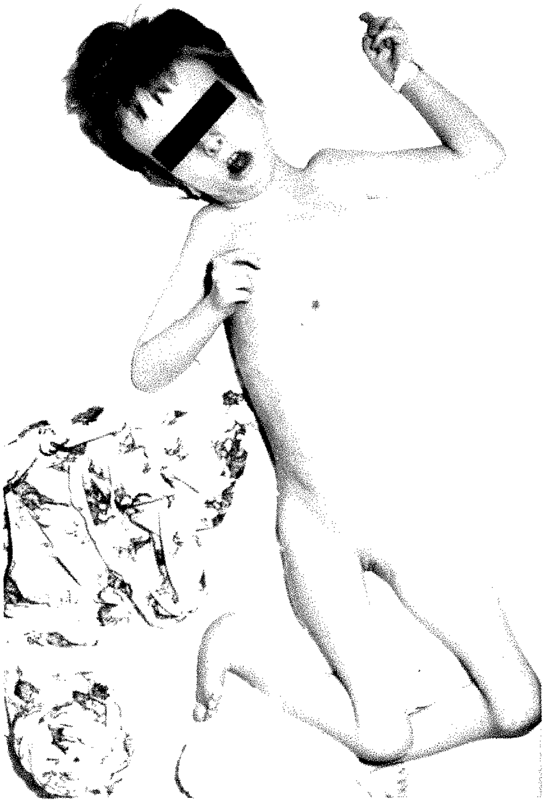

Fig. 1. A 10 year old girl with trisomy 18 syndrome. Muscle atrophy is evident. The extremities and fingers are in their usual attitude, but a small amount of active motion and full range of passive motion were present. There is rocker-bottom deformity of the foot.

toes of each foot were webbed and deviated laterally. Fingerprints were consistent with the pattern described in trisomy 18.[27] The results of blood chemical studies were normal. An electroencephalogram indicated a gross right temporal focus and secondary diffuse cortical disturbance. Further studies divulged no other causes of growth failure and the patient returned to the state hospital in an unchanged condition.

CHROMOSOME ANALYSIS

Only within the last few years have technical advances made possible the counting and grouping of the chromosomes (karyotype analysis) of human cells. By this means of examination several syndromes may be clearly differentiated, and some of the problems raised by the less refined process of sex-chromatin typing have been solved.

Material for analysis is most easily obtained from the blood. Leukocytes are subjected to modified tissue culture techniques and treated with a phytohemagglutinin to stimulate mitosis. Colchicine is then added to arrest the mitosis at metaphase and to inhibit spindle formation.[3] Suspension in hypotonic saline solution causes swelling of the cells. Gentle pressure may be used to accomplish separation of the chromosomes and, after straining, they can be photographed with high-power magnification to facilitate rearrangement and grouping. At the Denver Conference,[14] a system of nomenclature based on total length and arm ratio was formulated so that each chromosome pair could be identified by number or group. Tjio and Levan,[21] in 1956, showed that the normal human complement was 46 (23 pairs).

The presence of an extra chromosome will, therefore, be reflected in an increase in the total number of chromosomes (47 instead of 46), and the proper subgroup can then be determined by arrangement of the chromosomes according to the Denver system. The extra chromosome usually arises from a process of nondisjunction in the germinal cells of one of the parents, believed to be most often the mother. The normal meiotic process is one of reduction division, providing each of the gametes with one-half of that parent's complement of chromosomes. If any chromosome pair fails to separate, this specific chromosome will be doubled in this gamete, and, after uniting with the counterpart gamete, 3 chromosomes (trisomy) will take the place of the normal 2 of each type. If chromosome 21 is involved, mongolism results. Another syndrome is associated with an extra chromosome of Group 13–15.[10] If the sex chromosomes are involved, Klinefelter's syndrome will result from a doubling of the X chromosome in a male, or gonadal dysgenesis from a deletion of the X or Y

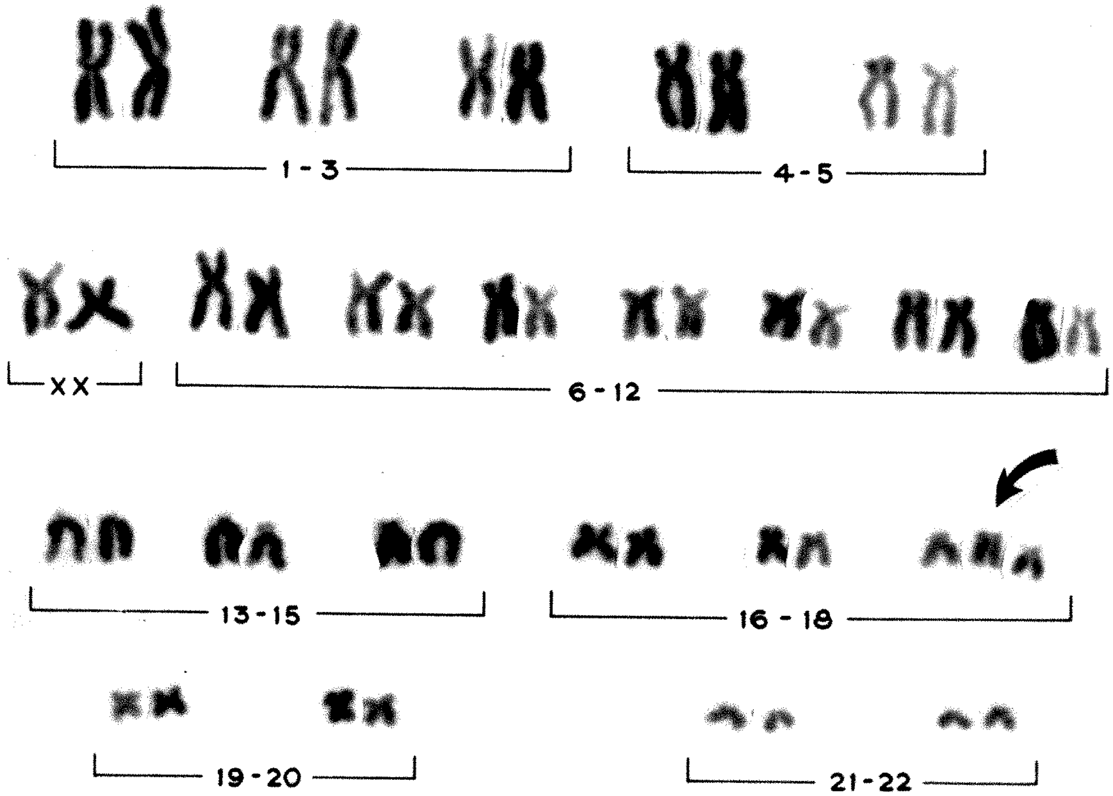

Fig. 2. Karyotype of the patient arranged according to the Denver system. Three No. 18 chromosomes were present (arrow).

chromosome. Other syndromes involving the X and Y chromosomes have also been described.[15,26]

The first report of trisomy 18 as a clinical syndrome was that of Edwards *et al.*[5] in 1960. These authors expressed the opinion that the extra chromosome was number 17 (in the Denver system); further study has shown that the trisomic chromosome is more likely number 18, but the individual chromosomes in the 16–18 subgroup are difficult to identify.[12]

A review of all the reported cases shows that the average maternal age was 32 years at the time of the affected child's birth. The basic defect in the trisomal syndromes is believed to result from nondisjunction in meiosis in the mother. In patients with other syndromes associated with nondisjunction (mongolism, Klinefelter's syndrome, and trisomy 13–15),[13,17] this increased age of the mother was also noted. In the present patient with a karyotype of 47 chromosomes, the extra one was chromosome 18 (Fig. 2). The mother's age of 32 years was consistent with the usual increased maternal age at the time of birth of patients with a nondisjunction syndrome.

CLINICAL FEATURES

Most of the characteristic features described in the trisomy 18 syndrome were observed in this patient. Her mental and growth retardation were striking. The high-arched palate, small mandible, and low-set deformed ears are characteristic of these patients, as are the short sternum and shield-like chest produced by widely-spaced nipples. Flexion of the fingers and foot deformities are also usually seen, the latter manifested as some variant of club or rocker-bottom foot. The lack of hypertonicity was the only unusual feature in this patient's syndrome. It was replaced by flexion deformity and joint laxity produced by muscular imbalance. The volume of muscle tissue was decreased notably. The exact type of her cardiac lesion is still unknown; it is consistent with pulmonary hypertension secondary to a ventricular septal defect. The 10 year survival is also unusual, being the longest known at this time.

ROENTGENOLOGIC FINDINGS

In few of the cases previously described has roentgenologic investigation been comprehensive. The most consistent abnormalities have been found in the chest. Slight to moderate heart enlargement with increased pulmonary vascularity was noted in most cases. Three patients underwent examination with contrast medium. Their respective roentgenograms showed ventricular septal defect with pulmonary hypertension, patent ductus arteriosus, and aortic coarctation with an aberrant right subclavian artery. Usually the only cardiac diagnosis possible was that of a left-to-right shunt. Eventration of the diaphragm was also noted frequently.

At times the roentgen examination failed to confirm the clinical suspicion. Decreased abduction of the hips was noted on physical examination in 12 instances, but on roentgen examination in 5 no abnormality was found. A small mandible thought to be present in 18 of the 24 patients was confirmed in only 1 of 7 in whom the mandible or neck was examined roentgenologically. The roentgen findings in all reported cases are shown in Table III.

Analysis of the roentgen survey of our patient suggests that the findings may be divided into two categories: (1) those possibly specific to this syndrome; (2) those consequent upon decreased muscle stress in what may eventually prove to be a primary disease of muscle. In general, the long bones showed the manifestations of decreased muscle action and isolated other bones showed more specific abnormalities.

The skull, cervical spine, and clavicles showed definite bone changes. The skull was long, although within the normal limits for this age. Prominent frontal bosses were

TABLE III

ROENTGEN FINDINGS IN TRISOMY 18 SYNDROME (INVESTIGATIONS IN 19 OF 25 PATIENTS)

Skull (10 examinations):	
Shallow or elongated sella	2
Prominent occiput	1
Defective ossification	1
Small mandible	1
Increased mandibular angle	1
Clavicle (3 examinations):	
Defective ossification	2
(No clavicular abnormality noted on 17 other chest examinations)	
Chest (17 examinations):	
Diaphragmatic eventration	7
Abnormal shape	2
Abnormal ribs	2
Short sternum	1
Sternum, decreased segmentation	1
Heart, enlarged	14
Increased pulmonary vascularity	11
Dextrocardia	1
Cervical Spine (4 examinations):	
Vertebral fusion	1
Thoracic Spine (3 examinations):	
Spina bifida, D9-10-11	1
Lumbar Spine (1 examination):	
Decreased anteroposterior diameter	1
Shoulder (1 examination):	
Subluxation	
Pelvis and Hips (7 examinations):	
Small pelvis	1
Femoral head dislocation	1
Hands (5 examinations):	
Short phalanges	1
Short fifth metacarpals	1
Angulation, fingers and wrists	1
No ossification of distal fifth phalanx	1
Pseudoepiphyses	1
Abnormal muscular shadows of hands	1
Feet (6 examinations):	
Equinovarus or rocker-bottom deformity	5
Vertical talus	4
Feet (*continued*)	
Calcaneovalgus deformity	1
Short toes	1
Cutaneous syndactyly	1
Double ossification centers ot calcaneus	1
Intravenous Urography (8 examinations):	
Hydronephrosis	1
Crossed ectopia with fusion	1
Bilateral ureteral reflux (cystogram)	1
Double kidney	1
Cardiovascular Contrast Studies (3 examinations):	
Angiocardiogram, ventricular septal defect with pulmonary hypertension	1
Aortogram, patent ductus arteriosus	1
Aortogram, coarctation of aorta with aberrant right subclavian	1
Skeletal Maturation (6 examinations):	
Normal	4
Retarded	2

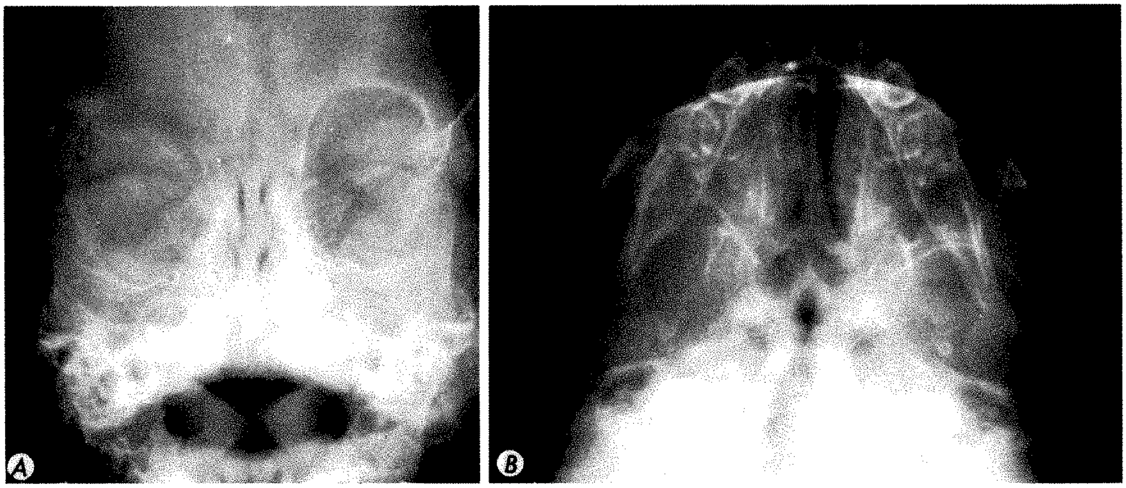

FIG. 1. (*A*) Posteroanterior roentgenogram of skull showing destruction of roof and indistinctness of superior orbital fissure of the right orbit. (*B*) Verticosubmental roentgenogram of skull showing loss of right greater wing of the sphenoid.

observe the patient. The patient was last seen on May 24, 1962 at which time there was moderate proptosis of the right eye with apparent vision in the eye and ability to follow light.

DISCUSSION

Juvenile xanthogranuloma is a rare disease primarily of infants and young children of unknown etiology, affecting chiefly the skin. There are, however, increasing numbers of reports of involvement of other organs such as the eye,[7,10] the mediastinum,[10] retroperitoneal space,[10] lung and testes,[2] and colonic mesentery.[8]

The skin lesions were first described in 1909 by McDonaugh.[5] He introduced the term nevoxanthoendothelioma. Senear and Caro[9] were the first to recognize the primary xanthomatous nature of the lesions. In 1954, Helwig and Hackney[2] reported 53

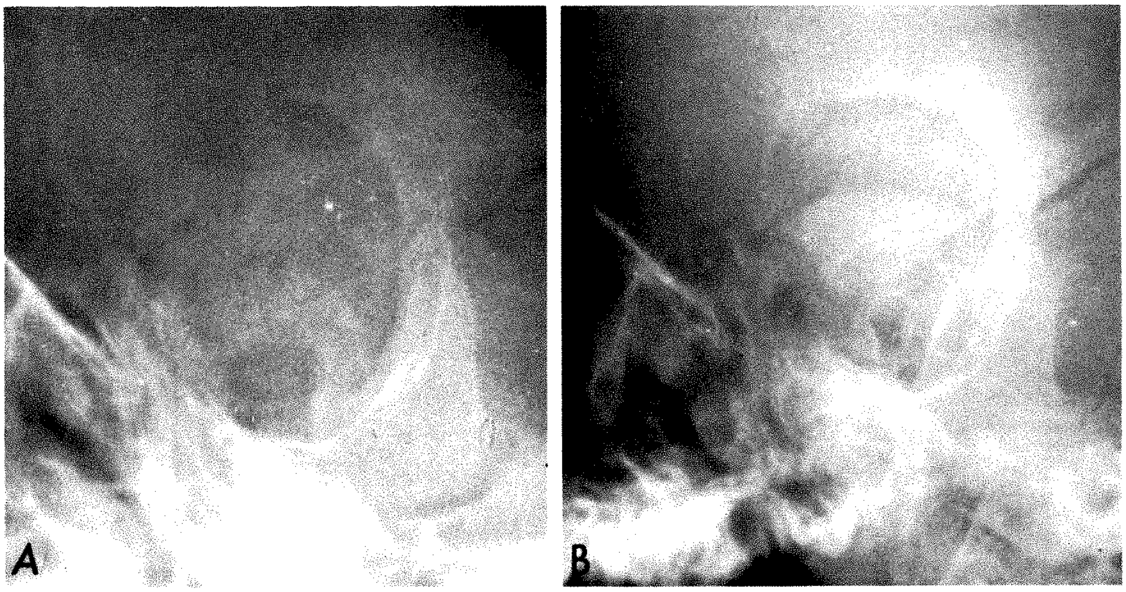

FIG. 2. Oblique posteroanterior roentgenogram showing large, indistinct right optic foramen and associated bone destruction. (*B*) Normal left optic foramen.

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JUVENILE XANTHOGRANULOMA OF THE ORBIT*

REPORT OF A CASE WITH BONE DESTRUCTION

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JUVENILE xanthogranuloma is a rare condition chiefly affecting the skin of infants and young children. The case reported here is the first to our knowledge with intraorbital yet extraocular involvement resulting in partial destruction of the orbit.

REPORT OF A CASE

This $4\frac{1}{2}$ month old white male infant was admitted to St. Louis Children's Hospital on March 28, 1962 with ptosis of the right eye and skin lesions present since birth. He was the product of an uneventful gestation and delivery. Growth and development were normal.

Abnormal physical findings were confined to the eye and skin. The right eye was exopthalmic with downward and lateral displacement of the globe. When the child was asleep there was definite corneal exposure. No Bell's phenomenon was present. There was excessive lacrimation and injection of the bulbar conjunctiva on the right. Both pupils reacted normally to light. There was definite limitation of upward movement of the right globe. Nystagmus was not present. The globe did not pulsate. On funduscopic examination the right disk appeared to be somewhat edematous.

In the left axilla there were 2 skin lesions measuring 2 and 3 cm. in diameter. Each was raised, having a yellow central portion and a pink periphery. The entire lesion was covered with a corrugated and atrophic surface. About these lesions were a number of 1 mm. or less, pink papules and smaller macules. The latter blanched on pressure. Similar lesions were noted on the lateral surface of the left upper thigh and the ring finger of the left hand.

The blood cell count, urinalysis, and serology were normal. The alkaline phosphatase, cholesterol, bilirubin, nonprotein nitrogen, total and fractional serum proteins, SGOT, and SGPT were also normal. Examination of the cerebrospinal fluid was normal.

Roentgenographic examination of the skull and orbits demonstrated bone destruction involving the roof and posterior lateral wall of the right orbit (Fig. 1*A*). A majority of the greater wing of the sphenoid on the right was absent (Fig. 1*B*). The right optic foramen and superior orbital fissure were indistinct (Fig. 2, *A* and *B*). Laminagrams of the orbits demonstrated the orbital lesions more clearly. A skeletal survey and intravenous pyelography were normal. A pneumoencephalogram demonstrated no intracranial mass or orbital encephalocele (Fig. 3).

On April 13, 1962 a right frontal craniotomy was performed at which time a yellow-white tumor mass was noted to involve the overlying dura and roof of the orbit and the retrobulbar fat. A superior orbital decompression was carried out.

Histologic examination of the retro-orbital and superior orbital tissue (Fig. 4*A*) showed focal nodular accumulation of foamy macrophages and histiocytes. No giant cells were seen. Sections of the bone fragments (Fig. 4*B*) showed similar histiocytic infiltration and osteoblastic activity. No Touton-type giant cells were seen. The general pattern was similar to that of the biopsied skin lesions.

The cutaneous lesions in the left axilla and thigh (Fig. 4*C*) showed large collections of histiocytes in the dermis. In sections of the left axilla, there was proliferation of rete ridges with infiltration of histiocytes to the tip of the papillae. In sections of the thigh, the epidermis was atrophic. There were many foamy histiocytes and multinucleated giant cells of Touton type. Peripheral infiltration of lymphocytes was present along with some capillary proliferation. Both the skin and orbital lesions were interpreted as juvenile xanthogranuloma.

The child made an uneventful recovery from surgery. External irradiation and/or steroid therapy were strongly considered but, in view of the orbital decompression and self-limited nature of this disease, it was decided to closely

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The general shortening of the shaft is associated with the decrease of growth and of maturation. The excessive tubulation is attributed to failure of periosteal bone growth, secondary to insufficient stimulus by muscle pull. In this respect, the disease would resemble arthrogryposis multiplex congenita, in which a primary muscle abnormality is assumed to produce bone and joint changes.

DIFFERENTIAL DIAGNOSIS

Differentiation of the trisomy 18 syndrome from arthrogryposis multiplex congenita should not be difficult if chromosomal studies are made. As yet, no cytogenetic aberration has been found in arthrogryposis. The pattern of multiple anomalies, marked failure to thrive, mental retardation, and cardiac and visceral involvement will distinguish trisomy 18 from arthrogryposis, which usually presents none of these and resembles trisomy 18 only in the muscular and skeletal abnormalities. In arthrogryposis the outstanding features are joint stiffness, deficient musculature, and contractures. These are in contradistinction to the hypertonicity and lack of fibrosis noted in young trisomy 18 patients and the laxity seen in our older subject. Also, in arthrogrypotic patients, mentality usually is normal.[8]

Trisomy 18 syndrome may be difficult to differentiate from amyotonia congenita, especially regarding the muscular abnormality. The marked flaccidity of the latter, however, has not been described with trisomy 18, nor have multiple structural anomalies been described as a usual feature of amyotonia congenita.[9]

Trisomy of one of the chromosomes of Group 13–15 has been associated with a similar picture of skeletal, cardiac, and neurologic abnormalities.[1,10,11,20,22] As yet, the cases reported have been too few to describe a specific set of characteristics. Some of these patients appear identical to those with trisomy 18 syndrome and at present differentiation is difficult without chromosome studies.

SUMMARY

Chromosome studies of infants and children with certain congenital abnormalities show that a characteristic syndrome is associated with an extra chromosome in Group 16–18. This abnormal genetic constitution probably results from a failure of normal disjunction in the germinal cells of one of the parents.

Most patients were females. Marked mental retardation, lag of growth, congenital heart defects, muscular defects associated with finger and foot anomalies, small mandibles, and deformed ears are among the abnormalities seen in children with trisomy 18 syndrome.

Most roentgenologic abnormalities are in the bones and can be related to altered bone modelling resulting from decreased muscular stress. The clinical and roentgen features of the oldest patient with this syndrome reported to date are described, and the clinical, pathologic, and roentgenologic findings in all previously reported cases are briefly reviewed.

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We are grateful to Dr. Grange Coffin of the Sonoma State Hospital, Sonoma, California, who brought this patient to out attention.

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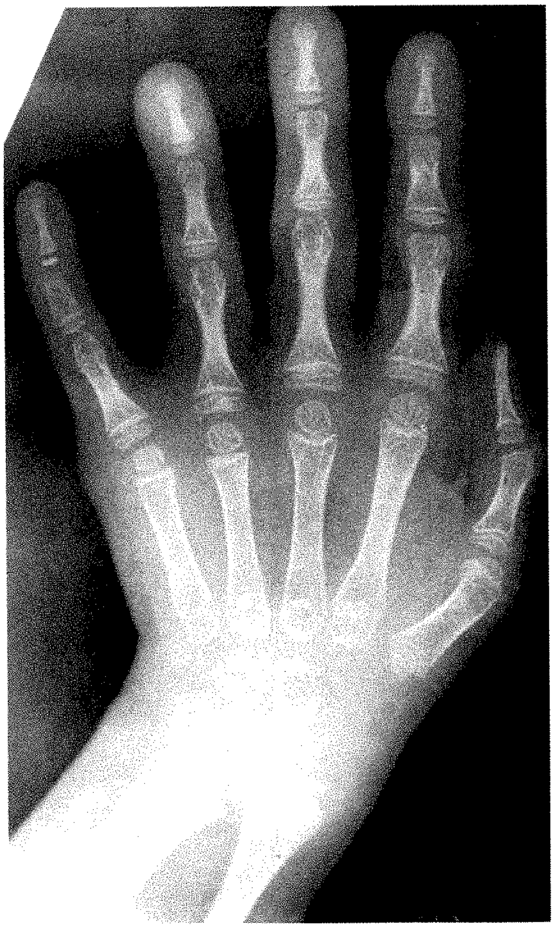

FIG. 10. The distal soft tissues of the hand are thickened and the phalangeal shafts are narrow. Pseudoepiphyses are present in the first three metacarpals. Decreased bone maturation is evident (estimated skeletal age 3½ years, chronologic age 10 years).

phalanges of the fingers and toes was seen, and the distal phalanges of the toes were minute. Pseudoepiphyses were noted in hands and feet. Bilateral vertical talus contributed to the rocker-foot deformity (Fig. 10 and 11).

Bone age estimates in the hands and feet indicated marked retardation of maturation. Many carpal centers had not appeared. The degree of retarded maturation was consistent with the growth retardation manifested by diminished length of long bones and the small stature. The bone age was estimated at 3½ years, a retardation of more than 6 years. The teeth did not appear to share this retardation.

These findings all suggest that several general processes are influential. A few specific findings have been described in the skull, cervical spine, clavicle, and heart. The other bone changes, however, can be ascribed to the effect of deficient muscular stress following impaired muscular development. This deficiency may be a primary feature of this disease or may result secondarily from disease of the nervous system. Periosteal appositional growth is most affected. This leads to a relatively normal appearance of the end of the bone, an area of endochondral growth, and considerable narrowing of the central shafts.

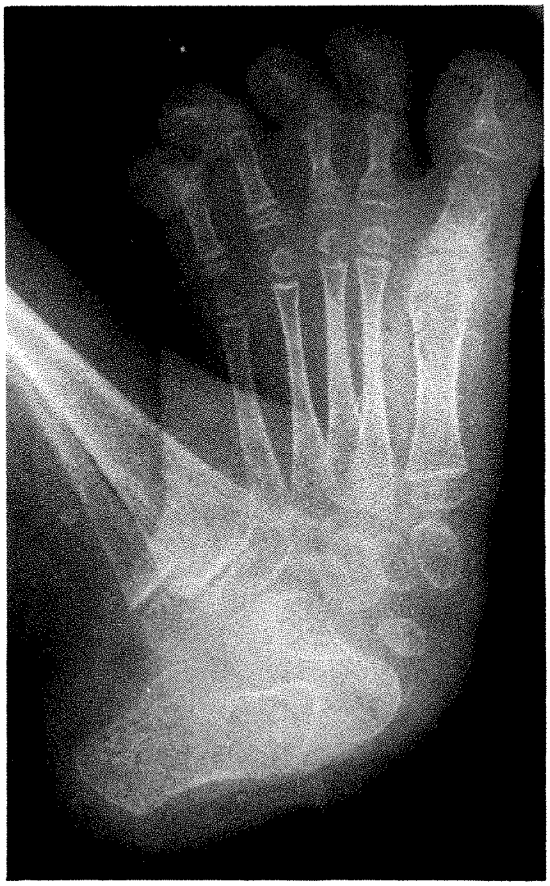

FIG. 11. Soft tissue thickening, excessive tubulation and pseudoepiphyses of the foot are evident. There is a vertical talus with talonavicular dislocation and the distal phalanges are small.

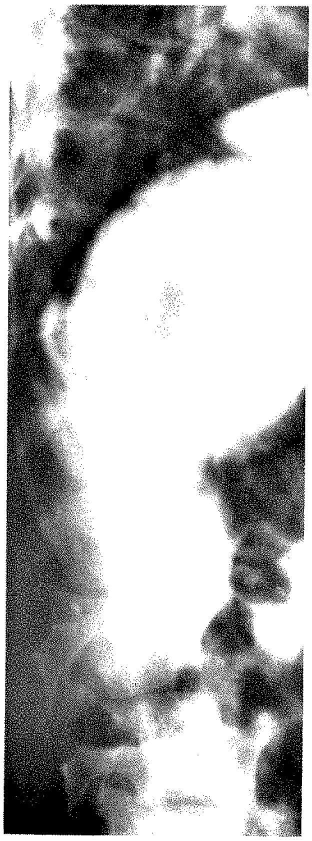

Fig. 8. The vertebral bodies are slightly decreased in height but markedly decreased in anteroposterior dimension. The anterior surfaces of the bodies are concave in the thoracolumbar region.

standing dislocation. Coxa valga of the femoral necks was present (Fig. 9).

The distal soft tissues of the fingers and toes were thick. Increased tubulaton of the

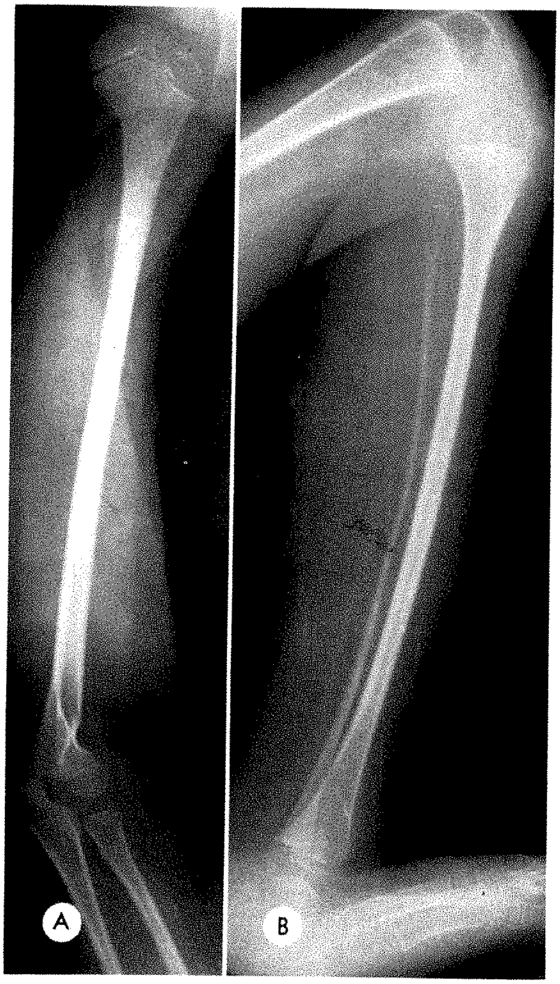

Fig. 7. (*A* and *B*) The total length of the humerus and tibia is decreased. The bones are excessively narrow in mid-shaft with marked diminution of the medullary space. General demineralization is present. The muscles are slender and almost of fat density. The subcutaneous fat is increased in amount. The humeral head is subluxated.

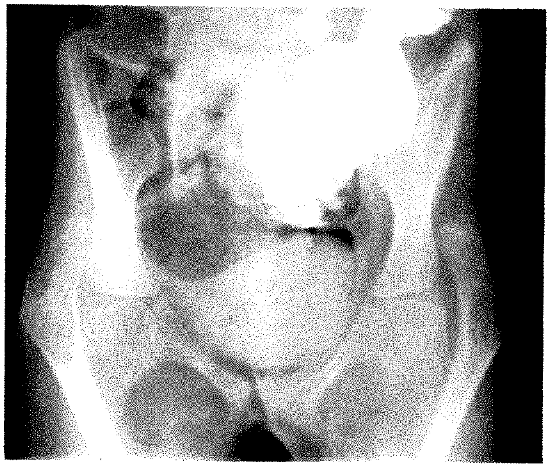

Fig. 9. There is rotation of the ilia medially, accentuating the small diameter of the pelvis. The sacroiliac cartilages are thick. The Y-cartilages and ischiopubic synchondroses have not fused. There is complete dislocation of the femoral heads with failure of formation of the acetabula. The small femoral heads and the coxa valga deformity are concomitant deformities.

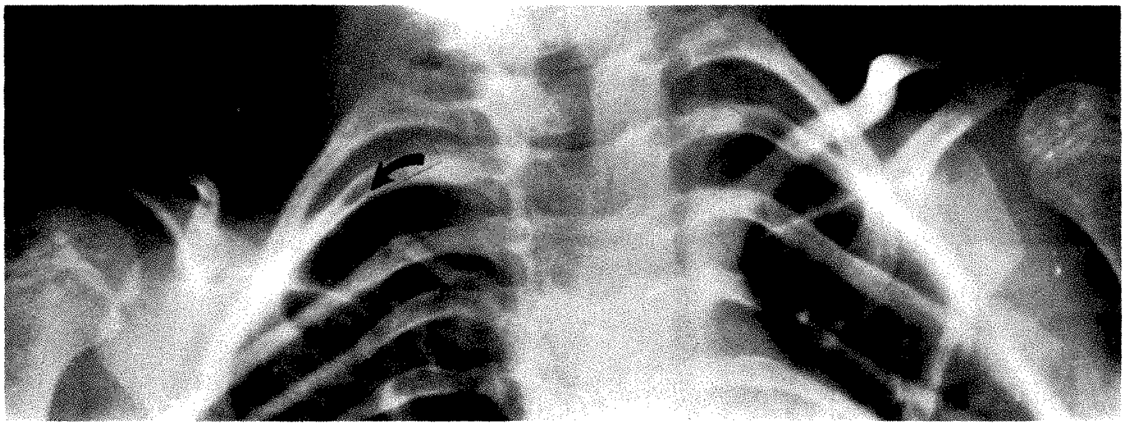

FIG. 5. There is a tripartite right clavicle with a bone defect in the central portion (arrow). The ribs are slender and irregular in contour and the humeral heads are mottled.

caliber of the metaphyses contrasted sharply with the excessive tubulation of the mid-shafts. Individual long bones of this 10 year old patient measured less in total length than in a normal 5 year old. Retardation in length was less than in caliber. Complete dislocation of the femoral heads and subluxation of the humeral heads can also be attributed to abnormal or deficient muscle pull (Fig. 7, *A* and *B*). The thin left clavicle and narrow ribs were also the result of deficient muscular stress.

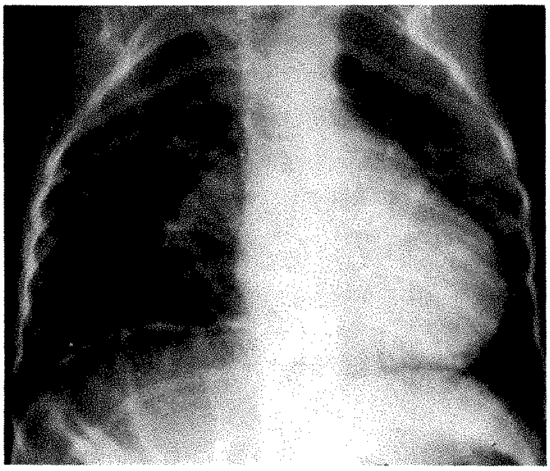

FIG. 6. The heart is enlarged in the transverse diameter. The right ventricle and pulmonary artery are dilated and the peripheral pulmonary vascularity is increased. The findings are those of a left-to-right shunt.

Slight scoliosis of the thoracic and lumbar spine was noted. In both areas the height of the vertebral body was slightly less than normal. This shortening was of lesser degree than that seen in the long bones. The anteroposterior diameter and interpediculate distance of the vertebral bodies were significantly decreased. These changes were more obvious in the lumbar than in the thoracic areas. The anterior faces of the vertebral bodies were concave in the lower thoracic and upper lumbar regions. Lumbar lordosis was increased (Fig. 8). The changes in the spine and extremities reflect a significant lack of periosteal apposition, probably a result of muscular weakness and decreased stress. Particularly is this evident when the diminished width from lack of appositional growth is compared with the more nearly normal height of the vertebrae, which is a product of endochondral ossification.

The pelvis was small and each half was rotated medially so that the apparent width of the ilia was diminished and the diameter of the obturator foramina accentuated. Nonfusion of the pubis and ischium was apparent, reflecting the retarded maturation of the skeleton. The sacroiliac cartilages were thick. The femoral heads were small and dislocated and no acetabula were identifiable, indicating long-seen. The calvarium was generally thin, with prominent diploic veins in the frontal bone, and the sella turcica was elongated and shallow. No definite abnormality of the mandible was seen. Although the angle was less acute than usually seen at this age, in view of the general retardation shown, a resemblance to a younger age conformation could be expected. The dentition was not retarded (Fig. 3).

The bodies of the second, third, and fourth cervical vertebrae were fused and the spinous processes were long and narrow (Fig. 4). The left clavicle was thin but not abnormal otherwise. The right clavicle was tripartite, with a thin medial segment, a hooked, shortened central portion, and a curved lateral segment (Fig. 5).

Except for the heart, visceral changes were not seen. The caliber of the small bowel was generally increased but the mucosal pattern and transit time were normal. The colon was dilated and redundant. No bowel diverticula could be shown. Intravenous urography demonstrated good excretion bilaterally with normal kidneys, ureters, and bladder.

The transverse heart diameter, right ventricle, and main pulmonary artery were enlarged. Pulmonary vascularity was increased. A diagnosis of left-to-right shunt was made (Fig. 6).

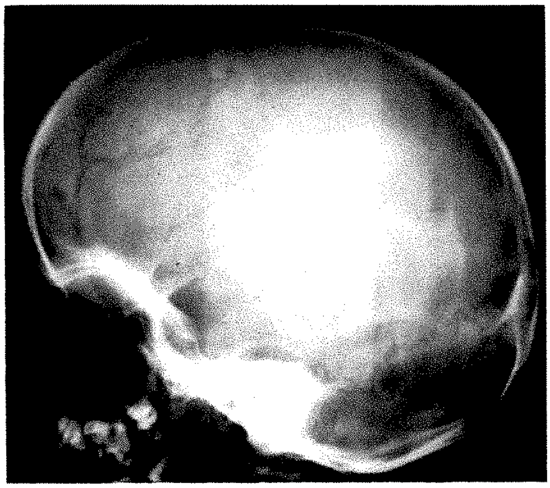

FIG. 3. The calvarium is thin with frontal bossing. There is an elongated and shallow sella turcica and the diploic veins in the frontal bone are prominent.

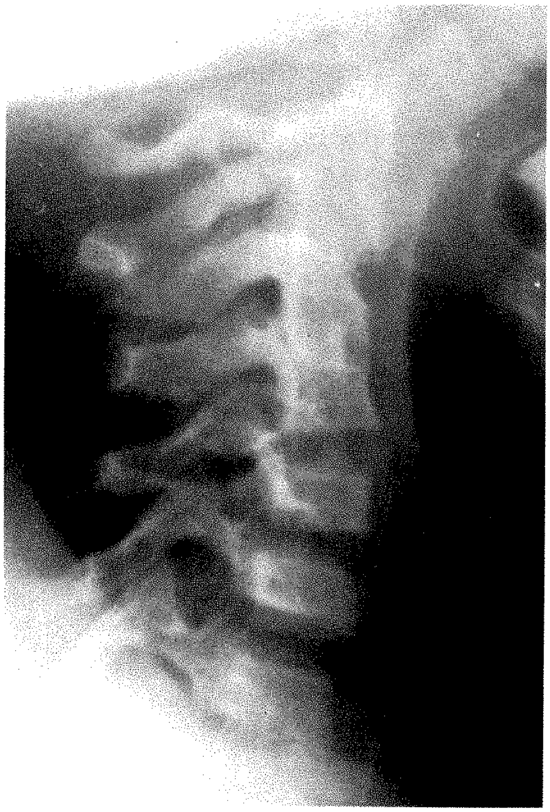

FIG. 4. The second, third, and fourth vertebral bodies are fused. The spinous processes are long and slender.

We are of the opinion that the other bone changes can be ascribed to a primary muscular defect. The total soft-tissue shadows in the extremities were much thinner than in the normal individual, with the muscle components markedly decreased. The fraction of the total shadow produced by subcutaneous fat was markedly increased. The muscular shadows were almost the same density as the fat, suggesting fatty replacement of many of the muscle bundles. The long bones at mid-shaft measured much less in total diameter than expected for their length. Most of this decrease was present in the portion normally occupied by the medullary space. The cortex itself was only slightly thinned in the mid-shaft. The more nearly normal cases and suggested that the term juvenile xanthogranuloma be used. Over 200 cases have been reported.[6,7]

The classic skin lesion is a small, circumscribed yellow papule. Early lesions may be pink. In one series[2] they were present at birth in one-fifth of the cases. They are usually multiple and found on the scalp and head. The trunk and extremities may also be involved. The lesions range in size from a few millimeters to 1.5 centimeters. Skin lesions may not occur until after the appearance of lesions in other organs. Spontaneous remission is the rule. There are no alterations in the serum lipids.

The exact relationship of juvenile xanthogranuloma to other lipoidal histocytoses or the reticuloendothelioses is unclear. There is evidence to support its separation into a distinct entity as: (1) distinct histologic differences exist; (2) transformation from one into the other has not occurred; (3) the course of the disease is benign with spontaneous remission; and (4) the iris lesions seen in juvenile xanthogranuloma have not been reported in the reticuloendothelioses.[7]

The histologic examination of the various lesions seen in this condition is quite accurate.[7] The skin lesion consists of a circumscribed collection of large, polygonal or spindle-shaped mononuclear cells in a groundwork of connective tissue. The cytoplasm is usually clear but may contain fat causing a foamy appearance. The lesions involve the corium. Occasionally, the subcutaneous tissue is involved. Touton-type giant cells are characteristic and are made up of lipid cytoplasm rimmed by nuclei. Eosinophils and newly-formed blood vessels may be present.

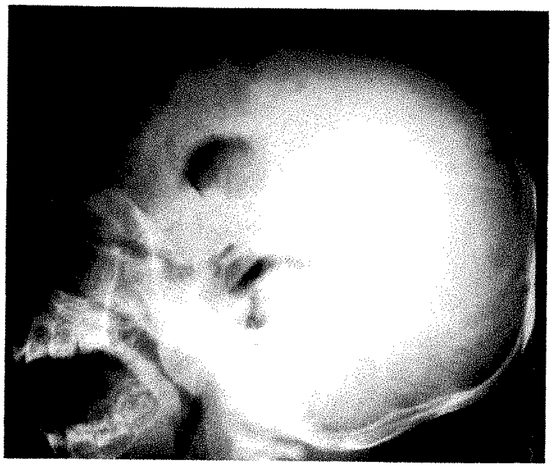

Fig. 3. Brow-up lateral pneumoencephalogram demonstrating no abnormalities.

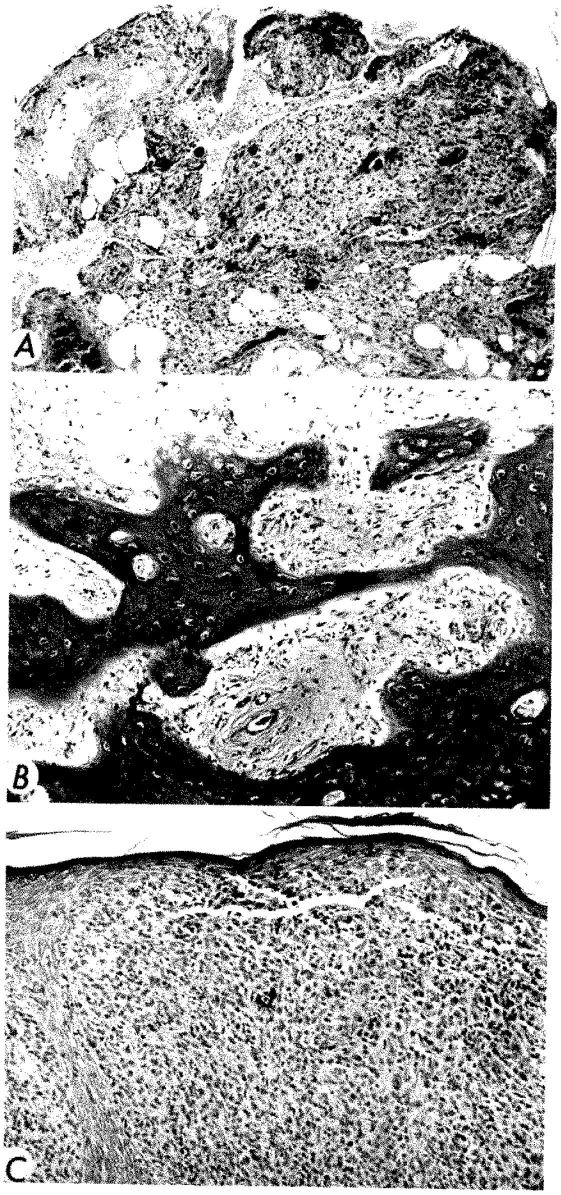

Fig. 4. (*A*) Characteristic lesion from soft tissues in the apex of orbit. (*B*) Invasion of bone. (*C*) Diagnostic lesion in skin biopsy. One Touton cell is present in the center of the field.

In a recent review Sanders reported 20 patients having intraocular involvement.[7] In all but 3 the onset of the disease was under 3 years of age. The iris was involved in every case and was usually described as being diffusely thickened with a muddy discoloration of the stroma. A localized iris mass was present in 3 patients. Spontaneous anterior chamber hemorrhage and secondary glaucoma were usually present. Where skin lesions were specifically looked for, they were present in 8 of 12 patients. None of these 20 had intraorbital yet extraocular involvement as in the patient being reported.

Although the disease is self-limited, radiation therapy has proved to be of benefit in those cases where further progression may be harmful to vital structures. The object of treatment to the globe has been to suppress histiocytic proliferation so that the complications of anterior chamber hemorrhage and glaucoma do not develop.

Hedges[1] treated one iris lesion with 50 r per treatment to 400 r over a period of 10 days (100 kvp., 15 ma., 24.5 cm. target skin distance, half value layer 3 mm. Al). The lesion cleared in 3 days and no recurrence had occurred after a 2 year follow-up. Maumenee and Longfellow[4] treated 2 patients. The first was given 600 r in a single dose to the iris and medial side of the globe (50 kvp., 20 ma., 1.8 cm. target skin distance, no filter, half value layer 0.28 mm. Al). The lesion regressed completely in one year. A small lens opacity was present on follow-up examination 5 years later. The second patient received 500 r in 100 r increments over 5 days (200 kvp., 20 ma., 50 cm. target skin distance, half value layer 1.0 mm. Cu). One year later, although there was no evidence of xanthogranuloma present, a central lens opacity had appeared.

Systemic and topical steroids may be given a trial. Diamox and miotics may also be used to treat glaucoma.[5]

Other causes for orbital destruction in this age group would include the reticuloendothelioses, particularly Hand-Schüller-Christian disease and Letterer-Siwe disease, metastatic neuroblastoma, neurofibromatosis with or without a meningo-encephalocele, leukemia, rhabdomyosarcoma, retinoblastoma, optic glioma, arteriovenous fistula, retrobulbar hematomas of scurvy and trauma, acute and chronic infectious disease arising in the orbit or paranasal sinuses, and benign orbital neoplasms such as hemangioma. If the characteristic skin lesions of juvenile xanthogranuloma are present, the correct presumptive diagnosis could be confirmed by biopsy.

SUMMARY

A case of intraorbital involvement of juvenile xanthogranuloma with partial destruction of the involved orbit is reported. Awareness of the condition and its associated characteristic skin lesions may avoid enucleation or surgical exploration.

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OBSERVATIONS ON THE CONSTITUTION OF THE PETROSA*

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THE French simply name the petrous bone "the rock" for in adults it is mainly ivory-hard bone. Orientation of its buried structure is very difficult and the reason why few radiologists achieve a mastery of its inner constitution.

In consequence, the detailed labyrinthine and attic projections of Stenvers, Owen,[17] and Mayer, have been slow to supersede those devised in the pre-antibiotic era to detect acute mastoiditis. Advances in precise microscopic aural surgery of cholesteatoma need the attic-additus views as urged by Compere.[3] Unfortunately, the minutiae so beautifully shown without distortion, by hypocycloid movement of the Massiot tomograph,[4,6] do not give the complete picture on which detailed orientation must be built. This uncertainty soon disappears by personal roentgenologic studies of midterm fetal skull bases.

These are peculiarly valuable for as Shambaugh[22] relates "developmental history of the ear is remarkable and without parallel . . . *the inner ear is the only organ that reaches full adult size . . . by mid term.*" This odd characteristic has been known since 1670 from a series of meticulous studies, especially the superb reconstructions of Bast.[2] Their roentgenologic counterparts are little explored. The fetal membranous labyrinth develops a bony shell *of adult shape and size*, which stands in roentgenologic relief for a period during fetal life. While Compere[3] notes that "at operation the otologic surgeon starts with a definite mental picture of the anatomy which will confront him," the radiologist thus has means to see the same.

We wish to show how the petrous bone is built up in adults from this stage. The complexities of the bone structure of the petrosal ridge disappear when correlated physiologically.

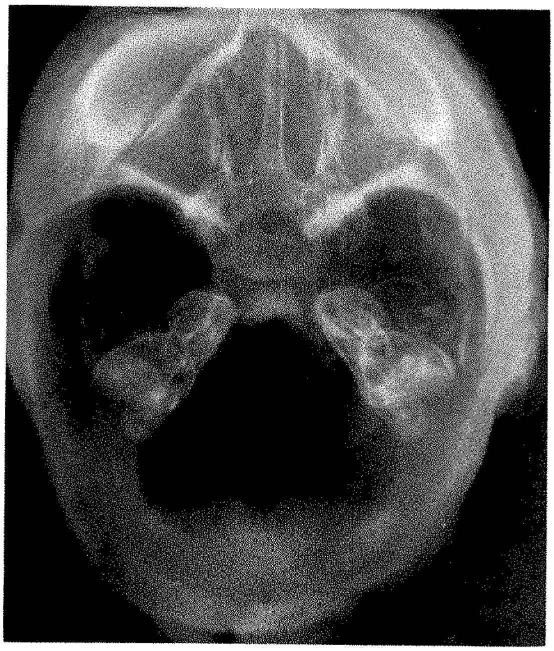

FIG. 1. Roentgenogram of fetal skull, the base of which is 18 cm. in circumference ($5\frac{1}{2}$ months). The bony labyrinths are almost adult in shape and size and are distinctly visible.

METHOD AND FINDINGS

Roentgenograms of a series of aborted fetuses serially representing the ages between 2 and 7 months were first surveyed. These confirmed Hill's[10] opinion that the earliest roentgenographic representation of bony labyrinth appeared in the third month. We found the clearest complete bony shell to be unobscured by adjacent ossification in fetuses of suboccipitofrontal skull circumference of 22 cm., that is around 24 weeks.[18] The lateral semicircular canal is last to ossify (Fig. 1 through 3, inclusive).

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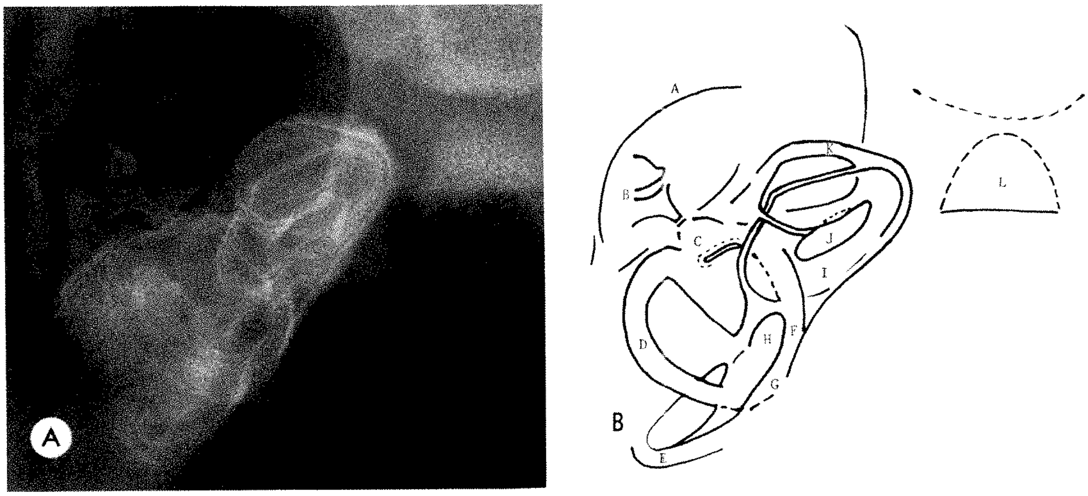

FIG. 2. (*A*) Right bony labyrinth, 18 mm. in length, of a 5½ month old fetus not yet obscured by petrous ossification. The horizontal semicircular canal is not yet ossified. (*B*) A—tympanic ring; B—malleo-incal joint; C—stapes footplate, the least ossified; D—lateral horizontal canal; E—posterior superior canal; F—anterior superior canal; G—endolymphatic sac hiatus; H—vestibule; I—basal turn of cochlear spiral; J—modiolus canal; K—second turn of cochlea; L—sella turcica.

Fixation of fetal skulls for various projections proved difficult. We thus made roentgenograms of twenty 4 cm. sections of 5 to 7 month fetal skull bases, cut inferiorly through the lower margin of the orbits, and parallel to the orbitomeatal lines. In this manner, unobscured views of the bony labyrinth were obtained. To our surprise, while the labyrinth is well known to reach adult size at mid-term, we found this maximum length to be practically uniform at 20 mm. from fetus to fetus. Many authors note its precocious development. Where an explanation is attempted, they regarded it as pre-empting of space by bone (Fig. 4). This is biologically improbable for bone is a notably adaptable structure in growth; the sphenoid grows quickly,[5] and even final size in bony orbit depends upon the presence of the soft developing eye. Why then does a labyrinthine sense organ grow independently?

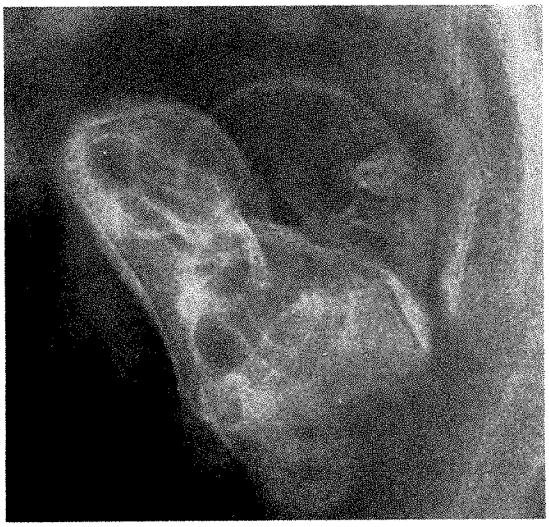

FIG. 3. Right bony labyrinth of a 5½ month old fetus, 18 mm. in length, almost touching the sella turcica. The circular tympanic ring partially underlies the inner ear at this age. The malleo-incal joint, additus ad antrum and modiolus aperture and the semicircular canals are distinct.

It is clearly not to provide hearing, for the middle ear is filled by gelatinous fluid for about a month after birth. Equally, the newborn infant is gravity bound and cannot alter its head position for several weeks. The roentgenologic clue of uniform bony labyrinthine size suggests that the cochlear end organ receptors may have a mathematically predetermined size derived from the frequencies they are to reproduce for conversion of sound components into separated nerve stimuli. Thus, unlike all other organs, its size need not be linked to the rate of body growth.

This is supported by other roentgenologic evidence, for the tympanum, bony tympanic ring, and ossicles also reach adult size in mid-fetal life. This contrasts with the external ear canal, which does not split from within out until the seventh month, and the pinna, which grows with the rate of the body in general. The fetal squamous temporal bone, however, is also relatively small and the bony external auditory canal does not grow until after birth. As a result, the tympanum and its bony ring tend to underlie the lateral portion of the fetal bony labyrinth[22] as illustrated here. At this age the mastoid process and petrous pneumatization have not developed to obscure these features.

Previous attempts on the problem of demonstrating bony labyrinth in its entirety for orientation have included metallic casts,[23,24] wire insertion,[20] fixation of land marks by injection of radiopaque media, silver impregnation,[16] followed by roentgenography and serial laminagraphy.[6] None are simple and all have required a very high degree of skill. Illustrations showing the orientation of the inner ear *in situ* are rare.[23]

ORIENTATION

The internal auditory meatus can be used as the key marker from which the probable positions of other structures can be mapped. What is often regarded as the lateral 1.5 mm. of the internal auditory canal is surrounded by the basal coil of the cochlea housing modiolus and the spiral ganglion; the medial remainder holds also the vestibular ganglion and the facial nerve. It seems likely that the relative positions of these bundles determine the normal variations in diameter noted between contralateral acoustic canals.[13] In adults the basal coil is just under 2 mm. in tubal diameter and 9 mm. in circumference. In the fetus the cochlear coil almost touches the sella turcica and only recedes with lengthening of the sphenoid (Fig. 1 through 3, inclusive). In the line of the petrous ridge, 5 mm. posterior to the center of the modiolus, lie the saccule, utricle, and endolymphatic duct. The latter emerges from a common bony vestibule and passes to the posterior fossa; 10 to 15 mm. posterior to the internal auditory meatus in the same petrosal ridge axis lie the semicircular canals. It is easy to recall that the semicircular canal system is separated from the posterior fossa by only 1.5 mm. of bone if one recalls that its perilymph circulation is probably cerebrospinal fluid derived from this closest source.

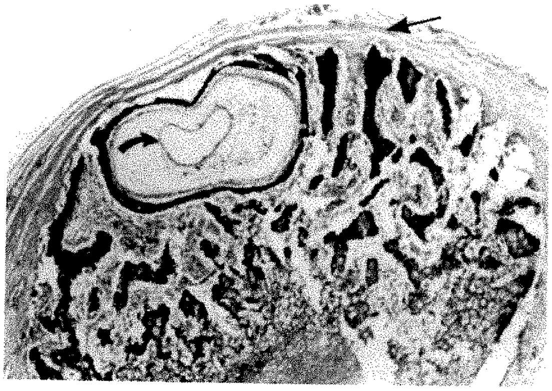

Fig. 4. Photomicrograph of the petrous ridge of a 4 month old fetus showing an epithelial semicircular canal (curved arrow) suspended in an arachnoid mesh and encased in bony labyrinth measuring 1.3×0.9 mm. Endochondral ossification has begun; the periosteum is still membranous (straight arrow).

COMPARATIVE ANATOMY

Willis[25] describes the internal ear "as one of the most speedy . . . of all the amazing transformations exhibited by the embryo," taking only those weeks of the second fetal month. Comparative anatomy helps to fix this complex structure in the understanding rather than by a feat of memory. The otocyst corresponds roughly with the statocyst of fish[15] with cartilaginous skeletons. This lateral line organ retains connection with skin, filled with water and has a lining of hair cells. It is a sensor of vibrations of very low frequencies, for fish are quite deaf in the human sense of sound.

The otocyst evolves posteriorly into semicircular canals, phylogenetically ancient structures, 1 in the lowest animals and reaching 3 in mammals. In humans

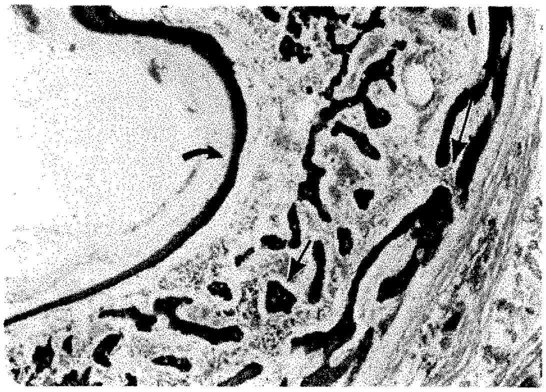

Fig. 5. Photomicrograph of the petrous ridge of a $4\frac{1}{2}$ month old fetus. Three patterns of ossification are present: continuous "endosteal" labyrinthine bone (curved arrow), endochondral bone with cartilaginous persistence (short arrow), and periosteal membrane bone in a porous layer (long arrow).

they have a predictive balance function. They provide stimuli indicating that the person will fall unless posture compensations are begun without delay. Their sensor tufts lie only in basal ampullary dilatations set to detect rotational shifts of fluid around the canals. The canals are thus escape mechanisms for fluid flow and not always in precise 90 degree planes to one another. It is easy to remember that they are oriented like a ship's binnacle lamp.

Connected anterior to the semicircular canals, the utricle senses linear centrifugal force. Function is still uncertain for the linked and apparently similar saccule. The otocyst becomes closed off and isolated, for example in amphibia, except for part of the first gill arch which modifies in higher animals to form a hooped chain of ossicles. This arc acts as a transformer while carrying the vibrations collected by the tympanum, diminishing their amplitude and increasing their intensity in the perilymph at the oval window. These pressure waves are sensed in the anterior auditory development from the otocyst. This evolves first in birds and reptiles as the lagena, a straight prolongation[11] of the equilibration chain in the petrous ridge. Its longer length in mammals is curtailed by two and three quarter turns of helical winding capping the internal auditory meatus. In adults the cochlea is $1\frac{1}{4}$ inches long and if unwound would reach into the petrous apex.

DISCUSSION

This entire series of structures develops a thin, smooth shell, or bony labyrinth, most usually detectable around the sixteenth week. Petrous ossification does not obscure it roentgenologically until after 6 fetal months. This bony rampart does not follow intimate narrowings of the inner epithelial tubes, but encloses a rim of extra space through which perilymph circulates. This fluid is probably cerebrospinal fluid, but no circulatory pathway is certain.[1] It is thought to enter through a fine cochlear "aqueduct" near the glossopharyngeal nerve sheath and, to a lesser extent, along perineural sheaths of acoustic nerves via the modiolus. Most is resorbed in the cochlea by the venules of the ligamentum spirale. A lesser exit has long been thought to be the fine prolongation of perilymph space around the slender endolymphatic duct which leaves the region of the utricle ending posteriorly in a blind sac beneath nearby dura.

This is the only portion of perilymph space not shut off by the bony labyrinth and which enlarges after birth. Ear infection travels by this route to produce cerebellar abscess. While temporal lobe abscess is twice as frequent in middle ear disease, it is usually a sequel of infected erosive attic cholesteatoma.

The epithelial otocyst induces regional chondrification,[25] excluding a perilymph space, and subsequent ossification of this matrix has appeared quite unique and complex. This is very understandable from Figures 4, 5 and 6, which show 4 apparently distinct patterns of ossification.[2,22] Conventionally regarded meanwhile these are:

1. A continuous bony labyrinth shell, enclosing the perilymph space with epithelial canals suspended by an arachnoid mesh. Such bone forms directly without preliminary cartilaginous scaffolding. It has been confusingly labelled "endosteal,"

THE DIAGNOSIS OF COLONIC AND TERMINAL ILEAL AGANGLIONOSIS*

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INFANTS with colonic and partial ileal aganglionosis, the long segment form of Hirschsprung's disease, frequently present with bizarre clinical findings, confusing roentgenographic images, and are often not recognized at surgery. In the majority of reported cases,[5,7,12] the correct diagnosis has been made only at autopsy.

We have observed 6 patients with this disease. As a result of early experience, criteria have been proposed that have enabled us to diagnose the last 2 cases preoperatively. These include (1) a colon of normal caliber though of a shorter length than usual, lacking the redundant loops and curves of the neonatal colon; and (2) a pattern suggesting ileal intussusception with associated small bowel distention.

REPORT OF CASES

CASE I. No. 160 82 25. This 2½ month old white male infant was seen in November, 1962. He was considered a normal full term infant. Meconium was passed at 36 hours of age. History revealed that he had moderate constipation with periodic diarrhea since birth. There was also bile-stained emesis, usually ½ to 1 hour after feeding. An upper gastrointestinal study done elsewhere at 1 week of age was considered normal. On admission he was found to be below his birth weight, pale and irritable. The abdomen was distended with palpable loops and the rectum was filled with soft stool.

Laboratory findings showed a mild anemia and a serum albumin of 2.5 gm./100 ml.; the remaining studies were normal. A plain roentgenogram of the abdomen (Fig. 1*A*) showed distended air and fluid filled loops of intestine. A clinical diagnosis of malrotation was considered and barium enema studies were made (Fig. 1, *B* and *C*). The colon was of normal caliber though the sigmoid lacked the normal redundant character seen in infants and the over-all length of the colon appeared shortened. Mild retention was seen on the 24 hour roentgenogram. To exclude the suspected malrotation as the cecum had not been identified on the enema study, an upper gastrointestinal study was performed the next day. The barium meal progressed to a loop of ileum that, on fluoroscopic examination, demonstrated repeated intussusception over a 20 minute period (Fig. 1*D*). A roentgen diagnosis of chronic recurring intussusception was suggested, possibly secondary to duplication.

At operation the next day, no intussusception was found. A shortened normal caliber colon was noted with slight thickening of the wall of the ascending colon. The terminal ileum appeared normal with minimal ileal dilatation proximally. A cecostomy was performed.

Postoperative leakage about the cecostomy developed and the small bowel dilatation increased; the patient was re-explored. Again, no obvious obstruction was found. Frozen sections were then obtained and aganglionosis of the colon and ileum was confirmed. An ileostomy was performed through a section of ileum that contained ganglion cells approximately 10 inches proximal to the ileocecal valve. Since the second operation, the patient has been rehospitalized almost monthly because of repeated diarrhea and distention. He weighed 9 pounds at the age of 9 months. If he survives, an ileoproctostomy is planned.

Comment. After two operations in a case where no obstruction could be found, suspicion of aganglionosis led to a frozen section study and the correct diagnosis. In reviewing the case, a marked resemblance of the findings on the barium enema examination (of normal caliber and short length) to 2 of the cases of Bowden, Goodfellow, and Munn[5] was noted. Their cases, the oldest being 3 months of age, died

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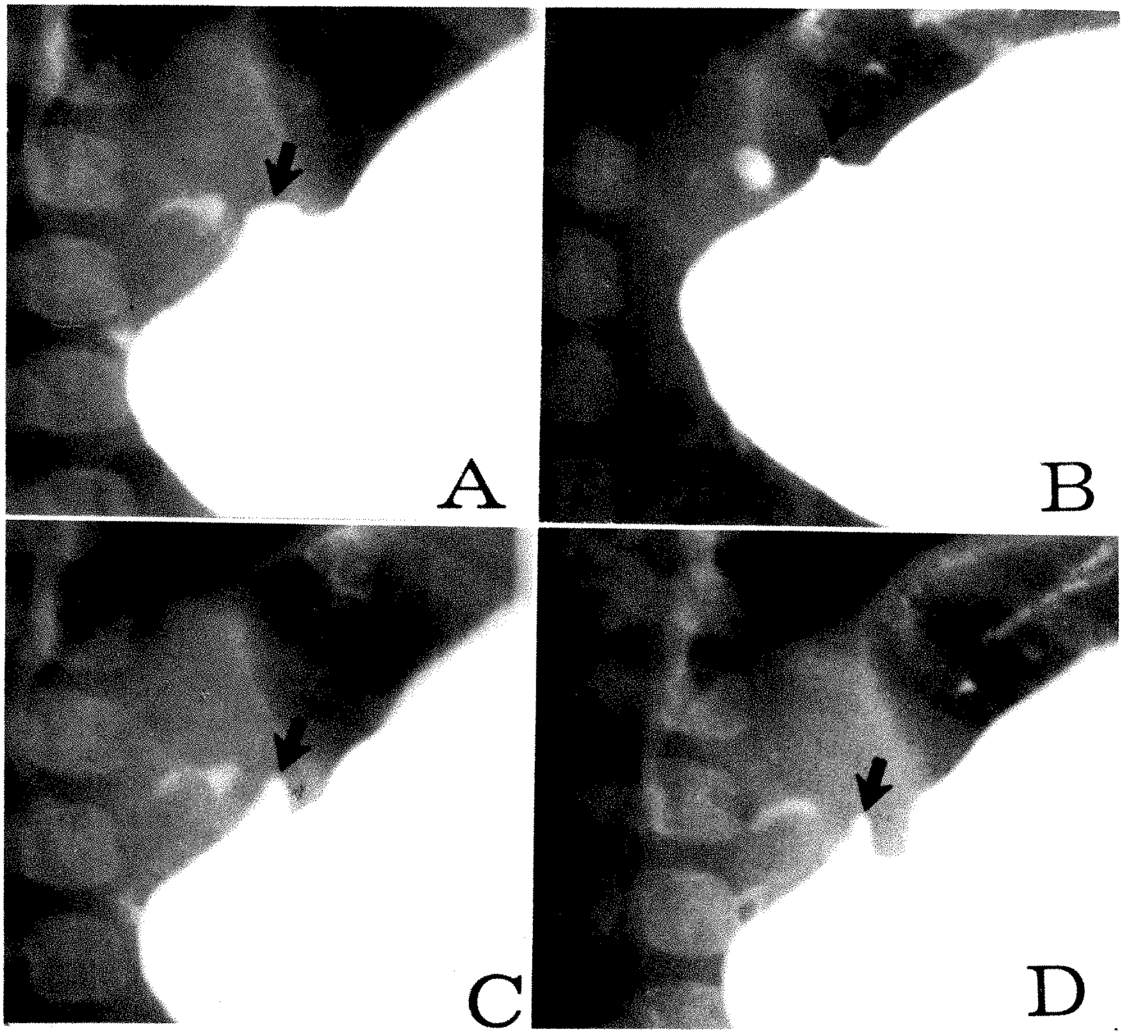

FIG. 8. (*A–D*) Spot roentgenograms taken in rapid succession in a case of hypertrophic pyloric stenosis. In *A* the peristaltic pouch is indicated (arrow). The pyloric tit is present in *B*, *C* and *D* (arrows), and has persisted for the 4 to 6 seconds necessary to expose the 3 films. A true pyloric tit will persist 2 to 8 seconds.

narrowed, elongated pylorus.

The observer's ability to visualize this interesting phenomenon depends entirely on his search for it. It is important that the stomach be deflated, either by tube suction or by "burping" during the roentgenologic examination. A stomach distended by secretions or air will not show sufficiently intense peristalsis and the antrum and pylorus may be obscured.

SUMMARY

1. A new roentgenographic sign of pyloric obstruction is described.

2. Diagnostic criteria are listed for establishing the diagnosis.

3. The pathogenesis and specificity of the sign are discussed.

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city of the pyloric tit. Thus far, it has been observed predominantly in patients with pyloric stenosis. This would be expected since this disease classically causes the pyloric elongation and concentric narrowing required for its production. The pylorus and first portion of the duodenum must be filled to satisfy the criterion that the tit stops in the mid-gastric antrum. It is not necessary, therefore, that it be used as a specific sign in pyloric stenosis since the filling of the pyloric canal will establish the diagnosis. However, the pyloric tit is helpful as it frequently is the first fluoroscopic indication of pyloric obstruction. Further experience may prove that the sign is more specific for pyloric stenosis than is presently thought.

The tit has been seen in 2 patients with pylorospasm. Its appearance and behavior were exactly the same in this condition as in pyloric stenosis except that it disappeared when the pylorospasm released. Characteristically, the pyloric narrowing and elongation seen with pylorospasm disappear within 5 to 10 minutes, enabling one to distinguish it from organic obstruction.

Occasionally, the normal peristaltic pouch may be so prominent as to simulate a pyloric tit. Differentiation is not difficult as the normal pouch will not persist, or become pointed, and it diminishes as it passes promptly to the distal end of the pylorus.

The tit has not been seen with other types of obstruction such as duplication cyst and ectopic pancreas. This is not surprising since ordinarily these conditions do not produce the required concentrically

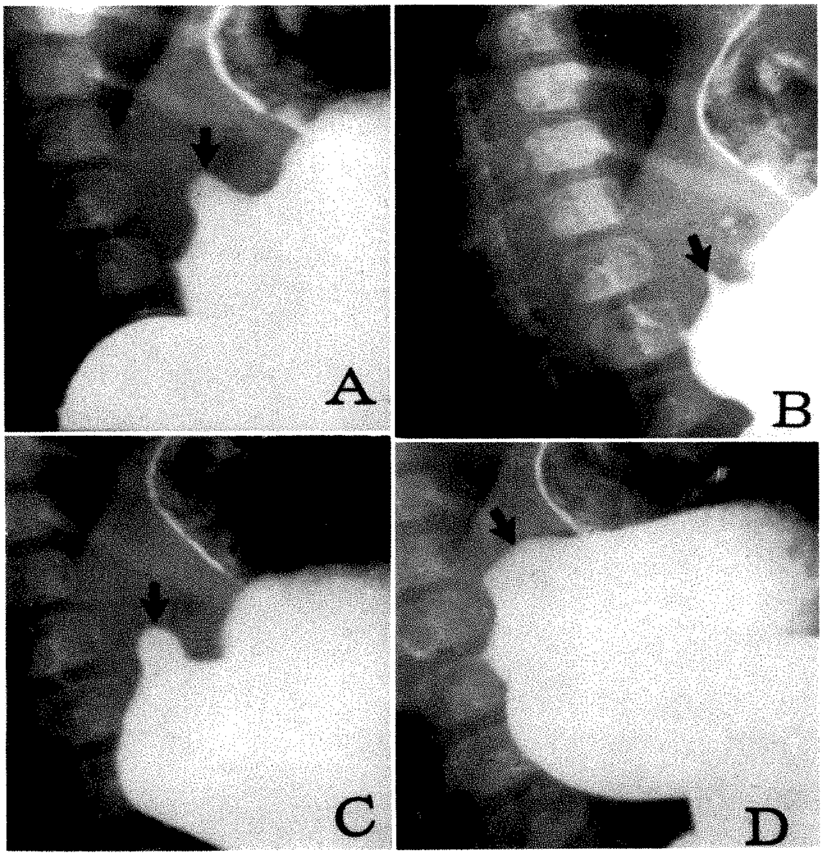


Fig. 7. (*A*–*D*) Spot roentgenograms in a case of hypertrophic pyloric stenosis. In *A* and *C* the wave is gradually pushing the peristaltic pouch downward (arrows). In *B* the pyloric tit is fully formed by compression of the pouch against the tumor (arrow). Note that the tit persists in the mid-antrum and does not pass downward. In *D* the tit has disappeared and another pouch is being formed (arrow).

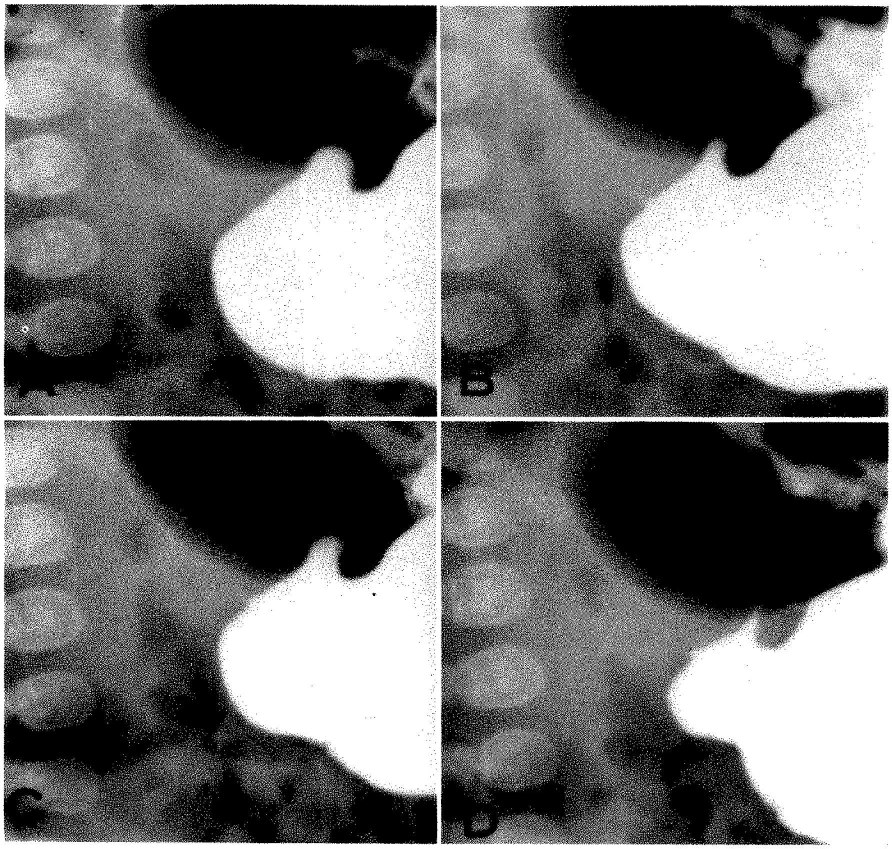
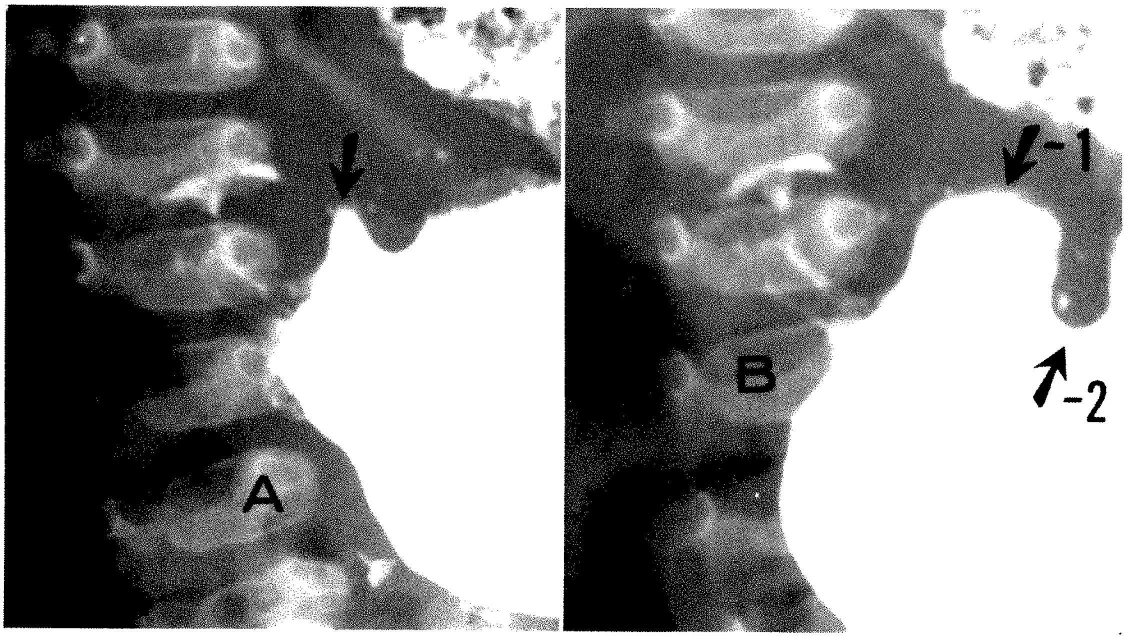


FIG. 5. (*A–D*) Spot roentgenograms of patient with hypertrophic pyloric stenosis showing conversion of a peristaltic pouch into a fully developed pyloric tit (arrows). *A*, *B* and *C* show intermediate steps and reveal the progressive narrowing and pointing of the pouch. In *D* the tit is fully formed.



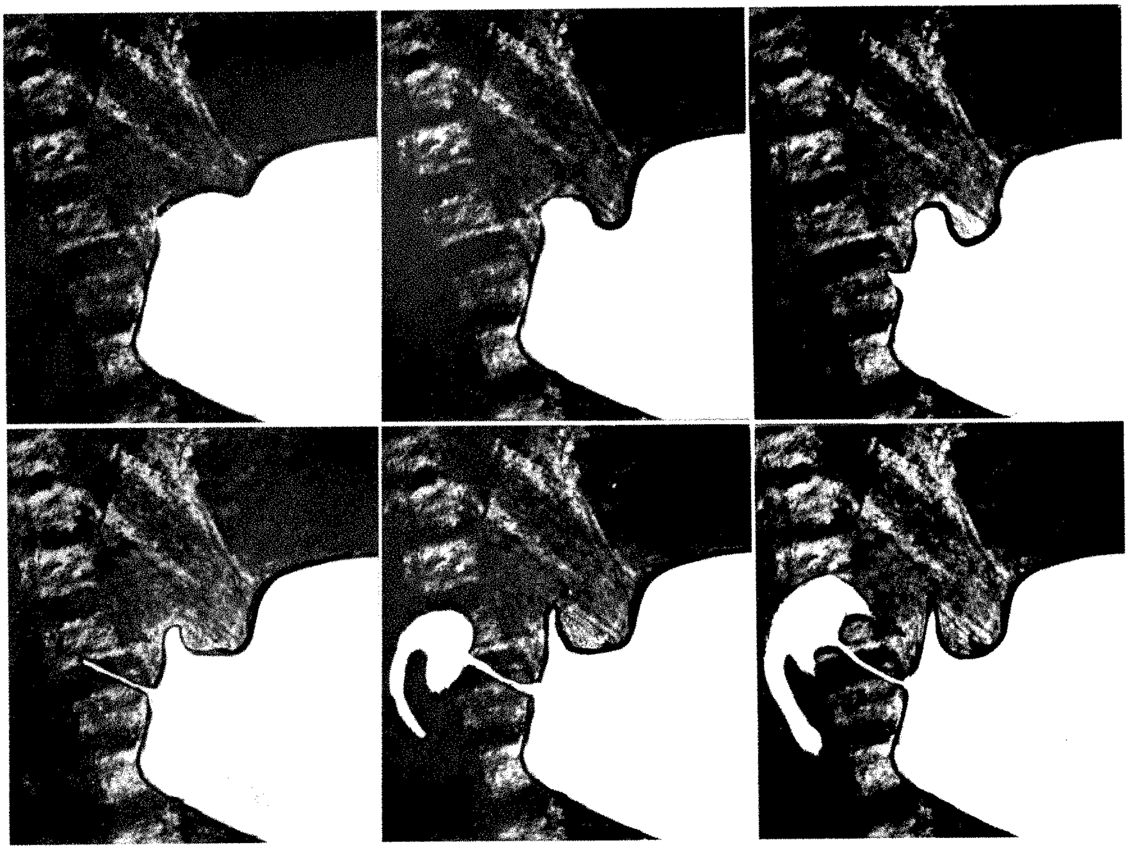


Fig. 4. Anatomic sketches showing genesis of pyloric tit in a case of hypertrophic pyloric stenosis. In the top sketches a peristaltic pouch has been formed and is progressing downward. In the bottom sketches barium is seen in the pyloric canal which is elongated and narrowed by the tumor, which in turn keeps the wave from progressing downward. The persistent peristaltic activity compresses the peristaltic pouch against the tumor, narrowing and sharpening it into the pyloric tit.

comes pointed because of an ironing out effect of it by the intensity of the wave (Fig. 6, *A* and *B*; and 7, *A–D*). When completely formed, the tit persists for several seconds as the peristalsis is inhibited from passing downward (Fig. 8, *A–D*).

It appears that a concentrically narrowed and elongated pylorus is a requisite for the production of a pyloric tit. Other types of obstruction, either because of eccentricity or shortness, will allow the wave to pass without producing a tit.

It is necessary that the following criteria be met before a peristaltic pouch be labelled a tit: (1) it must be pointed; (2) it must stop at a point in the mid-antrum; and (3) it must persist for several seconds.

DISCUSSION

An important consideration is the specifi-

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Fig. 6. (*A*) A tit is produced as a result of the force of the peristalsis pressing the pouch against the pyloric tumor (arrow). In *B* Arrow 2 indicates a deep peristaltic constriction and Arrow 1 the pouch produced by it.

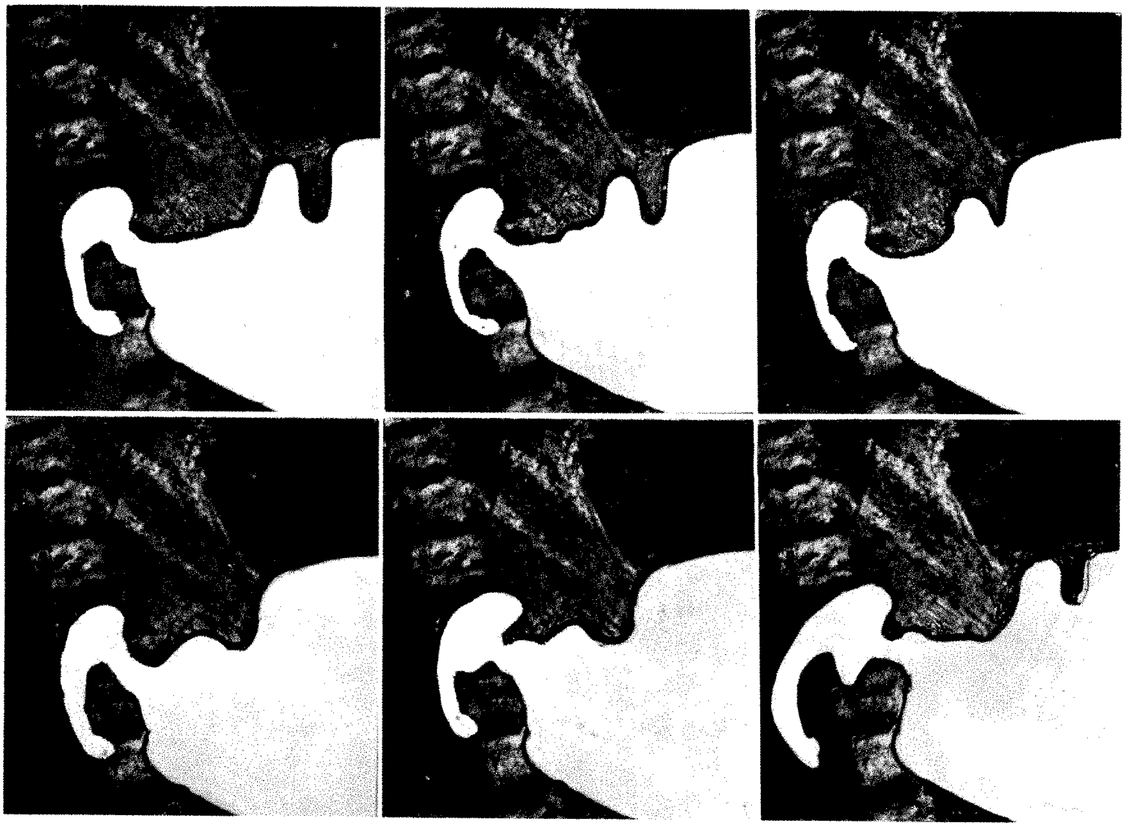

FIG. 2. Normal stomach. Sequence of sketches showing the pouch created by a peristaltic constriction. In the top sketches the pouch is well formed and is gradually advancing down the antrum. In the bottom sketches the pouch is diminishing into nothingness as it approaches the duodenum. In the last sequence another pouch has been formed to repeat the process.

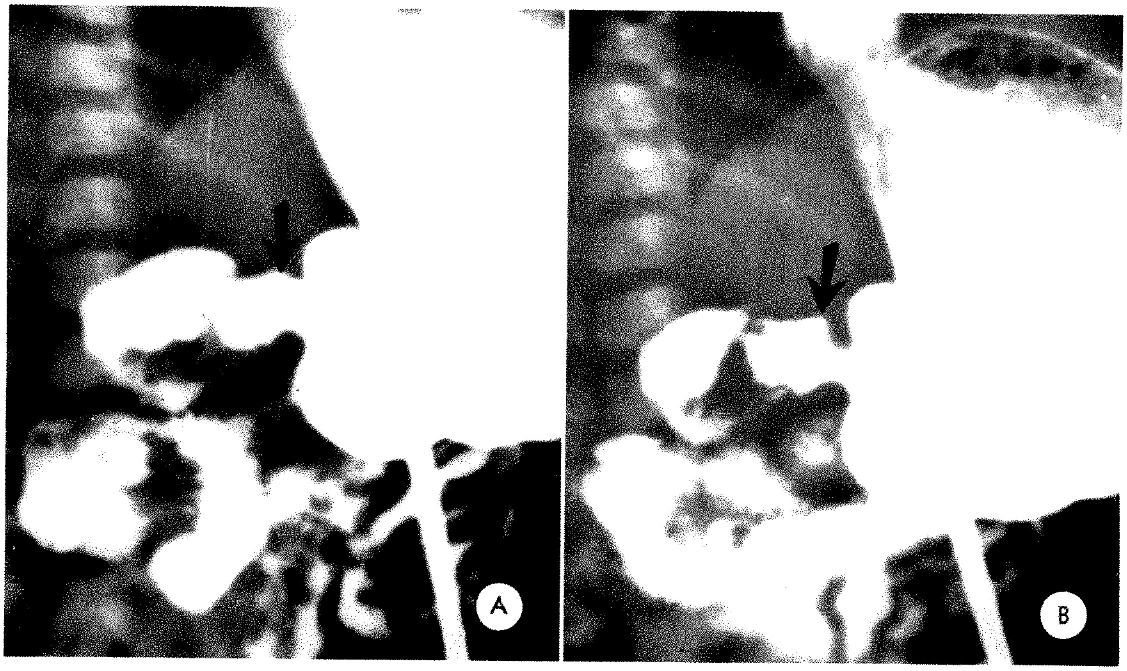

FIG. 3. Normal stomach. In *A* the pouch is indicated by the arrow. In *B*, taken a few seconds after *A*, the pouch is diminishing as it nears the duodenum.

THE PYLORIC TIT IN HYPERTROPHIC PYLORIC STENOSIS*

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THE pyloric tit (Fig. 1) is a projection from the lesser curvature of the gastric antrum seen in infants with pyloric obstruction. A review of the literature fails to reveal a description of this finding; however, Williams,[1] in 1963, stated "In the presence of pyloric obstruction, the terminal portion of each peristaltic wave persists as a hump on the lesser curvature of the stomach adjacent to the pyloric canal for several seconds, as if reluctant to depart and admit failure in its ability to empty the gastric contents."

A detailed description of the sign is merited because it is a frequent roentgenographic finding, has value as an aid in the diagnosis of hypertrophic pyloric stenosis, and often is the first indication of pyloric obstruction in babies.

INCIDENCE

Of 70 patients with hypertrophic pyloric stenosis of whom roentgenograms were made between 1953–1963, the tit was seen to some degree in 62 or 89 per cent. More significantly, it was present in 30 or 94 per cent of 32 patients examined since 1958 in which a specific search for the sign was made. In addition, 2 patients with pylorospasm exhibited the sign before the spasm released. It was not observed with other types of obstruction such as duplication cyst, ectopic pancreas, or duodenal obstruction.

PATHOGENESIS

Surgical exploration has revealed the stomach wall in the area of the pyloric tit to be normal. All of the patients operated upon had pyloric stenosis. The gastric wall above the tumor was soft and pliable with no projections to explain the tit. This would indicate that the projection is a pathophysiologic phenomenon.

Roentgenologic study appears to confirm the pathophysiologic explanation. In the normal stomach a haustral pouch is produced by a peristaltic wave (Fig. 2). The pouch gradually decreases in width and depth as the wave descends along the stomach wall and completely disappears as it arrives at the pylorus (Fig. 3, *A* and *B*).

The pyloric tit is believed to be persistence and accentuation of this normal peristaltic pouch in the presence of pyloric obstruction. The pyloric narrowing prevents the peristaltic wave from passing downward, and the pouch is converted into a pyloric tit by the persistent peristaltic activity attempting to push past the obstruction (Fig. 4; and 5, *A*–*D*). The pouch destined to become a tit is usually deeper than a normal one because of the increased peristaltic intensity. As the wave nears the obstruction, the pouch narrows in width and be-

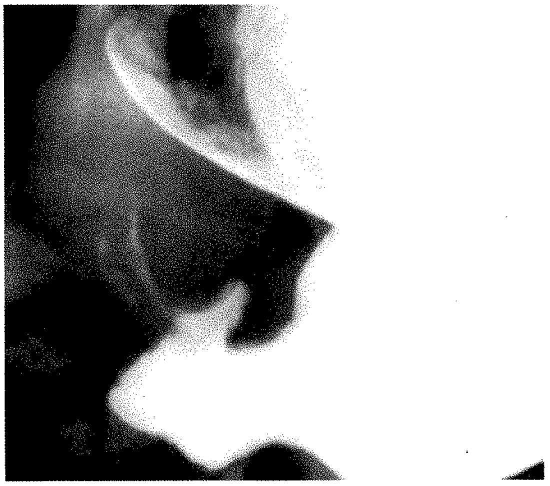

FIG. 1. Arrow indicates projection from lesser curvature of gastric antrum which is called the pyloric tit.

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both of these procedures are recommended for adults. In children with mild symptomatology, as in the 2 reported youngsters, conservative measures are totally adequate. Even in those children with more severe complaints, nonsurgical treatment, as advocated by Jackson and Hodson,[6] should probably prevail.

SUMMARY

Two cases of hepatodiaphragmatic interposition in children with gastrointestinal disturbances are reported. Speculation as to cause, associated symptoms, significance and treatment are reviewed.

Differentiation is made between temporary and permanent interposition, correlating the findings as noted in adults and children.

Intestinal interposition may be found in asymptomatic individuals, but more commonly in persons with gastrointestinal complaints. Few cases have been reported in children, whereas in adults this finding is noted with increasing frequency through the seventh decade.

In symptomatic children with hepatodiaphragmatic interposition, bed rest is the most effective means in alleviating acute abdominal complaints.

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but tending to disappear with supine positioning. Two of their 4 cases had permanent type interposition with supine positioning reducing the pain and distention.

The commonest symptom was abdominal pain with vomiting. Typically, pain occurred towards the end of the day when abdominal distention was maximal, being less frequent and less severe when the youngster was in bed. Other symptoms, less frequent, were anorexia, constipation and frequent passage of flatus.

Interestingly, in the 2 cases here reported, the common symptom was diarrhea. When the "gastroenteritis" disappeared the interposition was not evident. Aerophagia was not a recognized or obvious factor in these cases. A review of the cases in adults and the few reported in children led toward the following impressions: (1) intestinal interposition is more frequently seen in patients with gastrointestinal complaints, and (2) predisposing factors are a mobile right colon and readily displaced liver. Superimposed on these basic factors are (3) the effect of gravity permitting the liver to descend and intestine to ascend, and (4) the varying degrees of intestinal distention.

A further point of interest is that in our 2 cases frank abdominal pain was not a feature, whereas in Jackson and Hodson's study[6] 3 children had severe abdominal pain to the point where laparotomy was considered, but avoided because of the clearing of symptoms with bed rest when the supine position was assumed. They note that children with aerophagia and abdominal distention rarely complain of severe pain, and it may well be that only with intestinal interposition with some compromise of mobility (*i.e.*, torsion or incarceration) does frank pain present as a significant finding.

In our cases, the interposition was transient. The fact that there was abdominal cramping in Case I and a more prominent degree of interposition than in Case II suggests that the degree of distention and interposition might be contributing factors in the production of more pronounced symptoms.

In adults, Schenck[11] notes that patients who present with symptoms show an anomaly in the length of the transverse colon which is the reason the hepatic flexure is able to reach such a high position. Another factor he believes to be instrumental is colonic distention with rotation on its mesentery.

TREATMENT

In children, effective treatment is difficult to assess because of the lack of reported cases. This may be because of the rarity of interposition in children, the lack of sufficiently severe symptoms to require medical care, the failure to obtain roentgenologic studies to reveal its presence, or, as in adults, since it is occasionally seen in asymptomatic individuals, it probably is relegated to the realm of inconsequential or nondescript medical oddities.

Jackson and Hodson[6] emphasized that in symptomatic children, bed rest is the basic treatment. When aerophagia is recognized as being elemental in producing symptoms of abdominal distention with interposition and pain, the parents should be so informed and an attempt should be made to have the child refrain from this mechanism. Admittedly, such correction of aerophagia in a youngster might be of no avail, but an acknowledgment that this may be a causative factor in producing symptoms is to be noted. Carminatives and an abdominal belt are thought to be of little help. If diarrhea is a prominent feature, attempts to isolate an organism would seem indicated. Fluid and electrolyte imbalance was not a feature in any reported case in children, but conceivably this might occur and appropriate replacement therapy would then be required. Operative fixation of the colon is advocated by Rogers[10] in the symptomatic permanent type and Schenck[11] suggests that some form of hepatopexy in cases of "permanent incarceration" producing severe symptoms be accomplished;

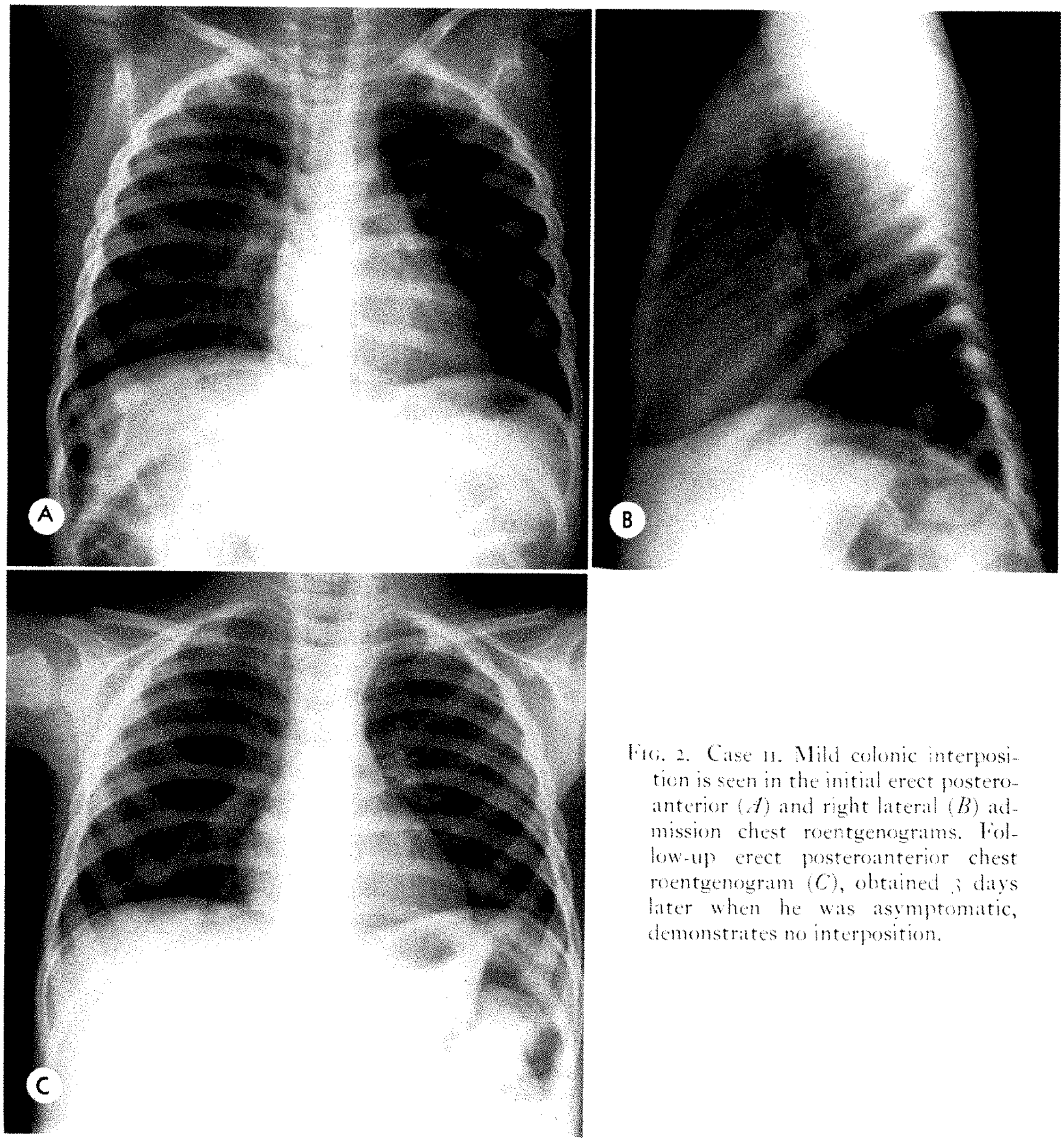

FIG. 2. Case 11. Mild colonic interposition is seen in the initial erect posteroanterior (*A*) and right lateral (*B*) admission chest roentgenograms. Follow-up erect posteroanterior chest roentgenogram (*C*), obtained 3 days later when he was asymptomatic, demonstrates no interposition.

per cent of 18,000 men above 65 years of age as opposed to 0.02 per cent in 25,000 men between the ages of 15 and 65.[13] This finding is less common in women. Kolju observed this condition in 0.14 per cent of 20,000 individuals, of which 14 of the 23 cases were of the permanent type.

In children, intestinal interposition may also appear with symptoms of pain, distention and vomiting. Jackson and Hodson[6] believe that the underlying mechanism is aerophagia in children who have an unusual mobility of the ascending colon and hepatic flexure due to the presence of an ascending mesocolon. Their explanation is that aerophagia causes abdominal distention and combined with the effect of gravity in the erect posture, the mobile right colon ascends into the subdiaphragmatic space and consequent inferomedial displacement of the liver results. In their 4 cases, distention of the alimentary tract was a prominent feature with the interposition demonstrable in the erect position, with slight gaseous distention which 3 days later was not demonstrated on the posteroanterior roentgenogram (Fig. 2*C*) when the child was asymptomatic. The clinical course in the hospital was uneventful, the infant being afebrile and "no stools in abnormal quantity or consistency" were noted during the hospital stay. Discharge diagnosis was nonspecific gastroenteritis, with temporary hepatodiaphragmatic interposition of intestine.

DISCUSSION

Two types of intestinal interposition occur: transient (sliding) and persistent (probably due to adhesions) with the right colon the more common interposer, although small intestine and omentum may also be present. The causes of interposition as outlined by Chousset and Chousset-Clause, in Bockus' "Gastroenterology"[2] are:

(1) *Intestinal factors:* (a) megacolon or abnormal accumulation of gas in the intestinal tract, causing upward displacement of the diaphragm; and (b) abnormal mobility of the colon of congenital origin.

(2) *Diaphragmatic factors:* (a) abnormally high diaphragm due to thinning of musculature or to musculature degeneration; (b) phrenic nerve injury or disease with paralysis of the diaphragm; and (c) changes in intrathoracic pressure, as in tuberculosis, empyema, etc.

(3) *Hepatic factors:* (a) ptosis of the liver; (b) small liver; (c) relaxation of the suspensory ligament; and (d) fixation of the liver due to adhesions associated with traction produced by the gastrohepatic ligament or perigastritis.

Although Kolju,[7] Linsman and Chalek[9] and Schenck[11] note that interposition may occur in adults without symptoms, a survey of reported cases lists a host of complaints which may be present in patients with this abnormality; namely, abdominal pain, abdominal distention, nausea, vomiting, flatulence, shortness of breath, pains in the substernal region and constipation. Kolju concludes that interposition occurs usually in people with gastrointestinal disorders. The incidence in children is unknown, but the occurrence apparently increases with age. It has been noted in 0.2

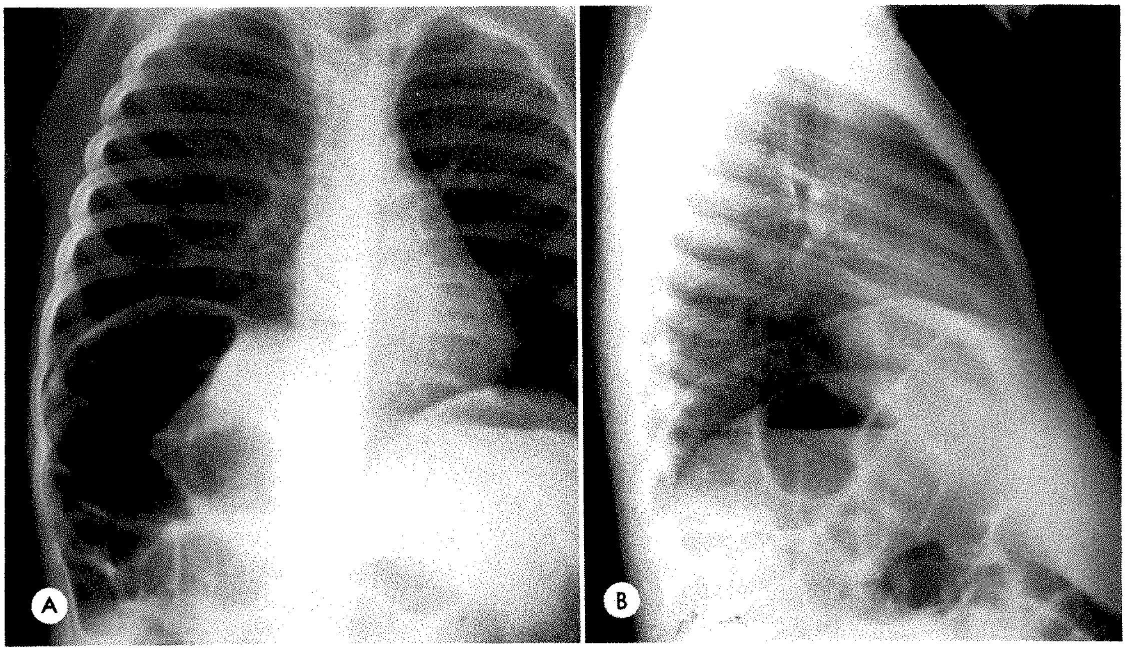

Fig. 1. Case 1. Note colonic hepatodiaphragmatic interposition with some intestinal gaseous distention in the erect posteroanterior (*A*) and left lateral (*B*) chest roentgenograms obtained on hospital admission when the patient was symptomatic.

HEPATODIAPHRAGMATIC INTERPOSITION IN CHILDREN

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HEPATODIAPHRAGMATIC interposition of intestine has been reported frequently in adults,[7,8,9,12,13] being first described by Cantini in 1865, according to Rogers.[10] The roentgenologic appearance was noted by Béclère in 1899,[1] but not until 1910, when Chilaiditi[4] surveyed the field and added 3 cases of temporary interposition, was this phenomenon more widely recognized, subsequently becoming known as Chilaiditi's syndrome. Uspensky[14] in 1928 recorded 8 cases of permanent interposition and 14 cases of temporary interposition, and since then multiple theories have been advanced in attempting to explain this abnormality.

In general, it is thought that this finding in adults, in itself, is of no clinical significance, but should be differentiated from free air beneath the diaphragm due to a perforated intra-abdominal hollow viscus or the presence of a subdiaphragmatic abscess. Rarely, intestinal interposition may present as an internal hernia of the small bowel through an aperture in the falciform ligament[4] or be associated with a volvulus of the sigmoid.[7]

Interposition of colon between the liver and right hemidiaphragm has been noted in children, occurring in megacolon[2] or in conjunction with aerophagia and abdominal distention.[6]

Recently 2 cases of children with intestinal complaints were observed, both of whom demonstrated intestinal interposition on routine erect chest roentgenograms. Because of the paucity of information regarding this finding in children, these 2 cases are reported, together with a review of the medical implications and aspects.

REPORT OF CASES

CASE I. A 3 year old boy was admitted to the Tucson Medical Center for mild diarrhea associated with intermittent abdominal cramping for the previous 9 to 12 months, with a recent onset of these symptoms. The mother related that there was no obvious blood or mucus in the stools. The child did not have nausea, vomiting or constipation. Physical examination was noncontributory. The laboratory findings were as follows: protein bound iodine 4.2 μg. per cent; feces negative for occult blood on 3 separate examinations; stool negative for ova and parasites on 3 examinations; glucose (fasting) 57 mg. per cent. Complete blood count and urinalysis were negative. Admission posteroanterior and left lateral chest roentgenograms demonstrated colonic interposition with distention (Fig. 1, *A* and *B*). On the third hospital day the patient's symptoms subsided and under image intensification it was noted that the colon and liver were in normal positions, both in supine and erect posture. He was subsequently discharged asymptomatic. The referring physician noted that the patient was living in a household of considerable tension and unrest. We were not impressed that he was an "air swallower," although this possibility was considered. Final diagnoses were diarrhea of unknown origin, possible gastroenteritis of psychogenic origin, and Chilaiditi's syndrome. A 4 month follow-up showed that the patient has continued to be asymptomatic.

CASE II. A 15 month old boy was admitted to the Tucson Medical Center because of diarrhea and "low-grade fever" of 4 days' duration. No temperature was actually obtained at home, but the mother stated that the patient felt warm and had frequent stools of no unusual color, smell or consistency. Physical findings were negative. Laboratory findings were as follows: stool, negative for ova and parasites 3 times; stool culture, negative for enteric pathogens 3 times; PPD and coccidioidomycosis skin tests negative; complete blood cell count and urinalysis negative. Admission posteroanterior and right lateral chest roentgenograms (Fig. 2, *A* and *B*) demonstrated intestinal interposition

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Table I

Patient	Race/Sex	Age* First Examination	Age* Last Examination	Interval*	Side	Roentgen Findings at First Examination	Roentgen Findings at Follow-Up
1. R.M.	W/M	14:9	16:7	1:10	R	Changes in the lower portion of right calyceal system, probably representing contusion in this area with decreased function	Normal
2. E.G.	W/M	14	16:9	2:9	L	Evidence of contusion of left kidney with bleeding. No definite evidence of kidney laceration	Normal
3. C.P.	W/M	11:7	14:2	2:7	L	Normal	Normal
4. R.C.	W/M	14:9	15:7	10 mo.	R	Defects in the right renal pelvis representing blood clots. Also straightening of upper portion of right ureter, probably due to surrounding hemorrhage and reaction to the injury	Normal
5. J.M.	W/M	9:4	11:9	2:5	R	Right renal contusion with poor delineation of the excretory system and probably filling defect in the right pelvis representing blood clots	Normal
6. J.F.	W/M	6:9	20:7	13:10	R	See case below	See case below
7. R.Y.	W/M	14:8	19:3	4:7	L	Normal	Normal
8. A.R.	W/F	5:2	7:10	2:9	R	Probably normal right calyceal system. Nonvisualization of left calyceal system thought to be agenesis of kidney	Normal
9. G.F.	W/M	10:10	13	2:2	R	Poor visualization of right calyceal system but was considered to be within normal limits. Could be result of poor preparation or trauma	Normal
10. J.T.	N/M	11:7	13:2	1:7	R	See case below	See case below
11. J.H.	W/M	13:4	16	2:8	L	Contusion of left kidney with visualization of only the lower calyceal group and ureter	Normal
12. S.T.	W/M	12:9	14:3	1:6	R	Findings were compatible with contusion of the right kidney	Normal
13. K.E.	W/M	7:9	11:3	3:6	L	Intravenous pyelogram thought to be within normal limits	Normal
14. M.P.	W/M	12:5	13:9	1:4	L	Findings compatible with hematoma of parenchyma of left kidney without evidence of rupture of calyceal system itself	Normal
Median		12:1	14:25	2:6			

* Year: month.

opening the peritoneum, a considerable amount of bloody fluid was encountered. A large hematoma was noted in the retroperitoneal region surrounding the right kidney. The hematoma had dissected down to the right gutter retroperitoneally. A long laceration, about 2 inches in length, was noted on the anterior aspect of the kidney extending from the region of the hilus to the lower pole of the kidney. An additional laceration, 1 inch in length, was observed in the posterior aspect of the inferior pole of the kidney (Fig. 1). It was thought that the lacerations did not involve the renal pelvis. Oxycel sponges were placed in the laceration and large stay sutures were placed through the kidney substance and tied.

Roentgenographic examination prior to surgery had demonstrated a lack of definition of the right kidney. In addition, there was a fracture of the right ulna and fracture of the seventh to the eleventh right ribs. Postoperatively, there was a brief episode of paralytic ileus but the urine was free of albumin and red blood cells within 9 days. Two weeks after the injury, an excretory urogram demonstrated distortion of the right calyceal system which

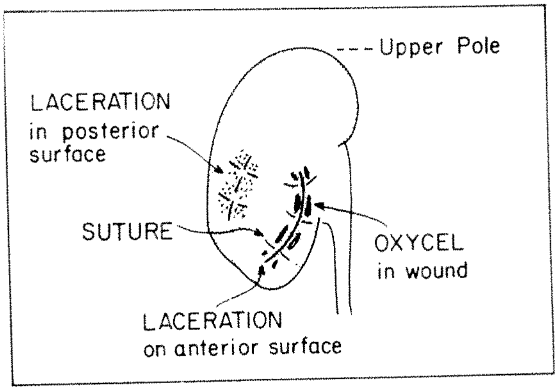
Upper Pole
LACERATION in posterior surface
SUTURE
OXYCEL in wound
LACERATION on anterior surface

FIG. 1. Case 6. Male, aged 6 years 9 months. Diagram of extent of injury and nature of repair. Copied from surgeon's note in hospital chart.

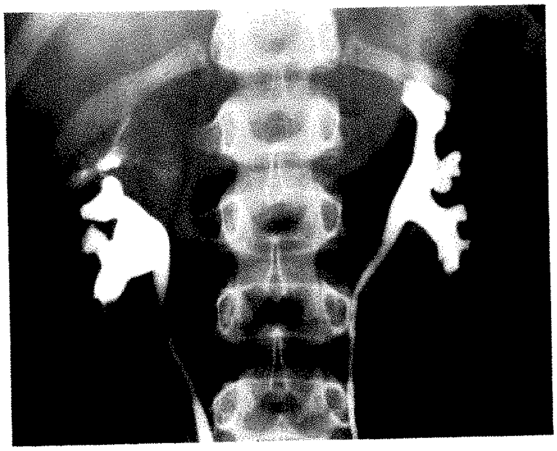

FIG. 3. Case 6. Retrograde pyelogram 2 years after injury. The superior calyceal system on the right is distorted and shrunk when compared to configuration in Figure 2.

was thought to be a consequence of a contusion, laceration and repair (Fig. 2). A repeat intravenous pyelogram on August 25, 1950 (15 months after injury) demonstrated additional change in the right renal pelvis and calyceal system with narrowing of the upper major infundibulum. Slight blunting of the lower calyceal system was noted together with some increasing fullness of the pelvis. A retrograde pyelogram was done May 12, 1951 (2 years after the injury) and demonstrated marked narrowing of the upper minor infundibulum with blunting of the minor calices (Fig. 3). Otherwise, no significant changes had occurred since the previous intravenous pyelogram. The most recent follow-up examination was done on March 2, 1963 (13 years 10 months after injury) at which time calcification was noted in the lower portion of the right kidney at the site where the laceration had been present and packed with oxycel sponges (Fig. 4). The calyceal system demonstrated no changes in comparison with the previous examinations. The outline of the kidney had been indented near the site of the calcifications since the examination 15 months after the injury.

CASE 10. J.T., a Negro male, aged 11 years 7 months, was admitted on October 27, 1959 after being struck on the right side by an auto-

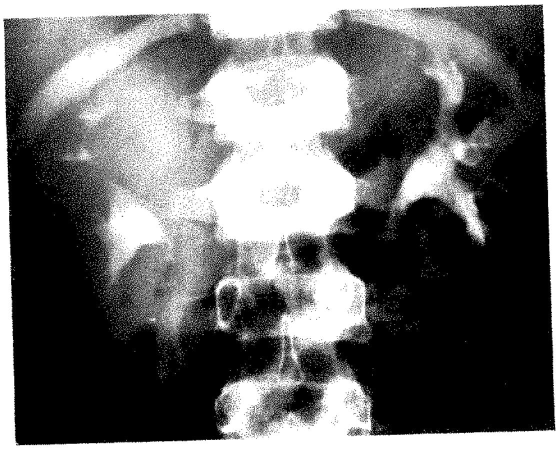

FIG. 2. Case 6. Excretory urogram 2 weeks after injury and repair. The infundibulum to the superior group of calyces on the right is narrowed; the middle and inferior groups of calyces are compressed—edema? hematoma?

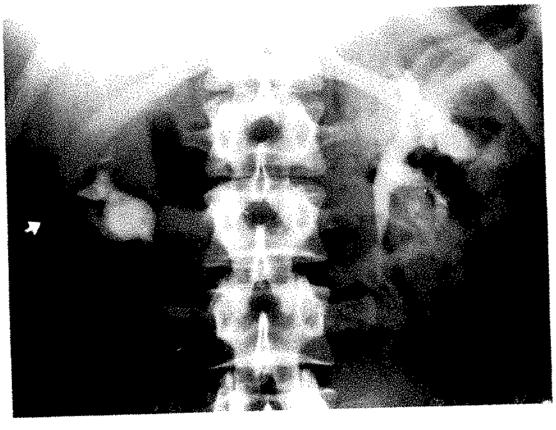

FIG. 4. Case 6. Excretory urogram almost 14 years after injury. The distortion has not changed, but calcification has appeared in lower half of kidney, presumably in area of repair. Patient clinically healthy.

mobile. He was admitted to another hospital and when hematuria was noted he was transferred to Children's Hospital. On physical examination, his pulse was 96 per minute, respirations 24 per minute and his blood pressure 110/70. There was some tenderness in the right upper quadrant of the abdomen. The hemoglobin was 11.5 gm., the white blood cells numbered 11,700 per cubic milliliter, and 2 to 3 red blood cells per high power field were noted in the urine. An intravenous pyelogram on admission demonstrated fractures of the right tenth and twelfth ribs. There was evidence of rupture or contusion of the upper pole of the right kidney with some extravasation of contrast material into the renal parenchyma, but not into the perirenal tissue (Fig. 5). On November 5, 1959, intravenous pyelography was considered normal (Fig. 6). The follow-up examination was done on May 5, 1961 (1 year 7 months after injury) and showed minor changes in the right upper pole with some shortening of the superior major infundibulum in comparison with the previous examination (Fig. 7). The renal outline, however, was not appreciably altered.

DISCUSSION

In our Case 6, injury to the right kidney was quite severe as demonstrated at the time of operation. The lacerations were limited to the lower half of the kidney, both on the anterior and posterior aspects. Although it was not demonstrated at the time of operation, it was very likely that some injury to the upper portion of the right kidney or its blood vessels had taken place at the same time. Surgical intervention was restricted to the lower pole of the kidney. Nevertheless, at the examination 13 years after injury, changes were present in the entire kidney and calyceal system, including calcification in the lower portion. The calcification was probably occasioned by

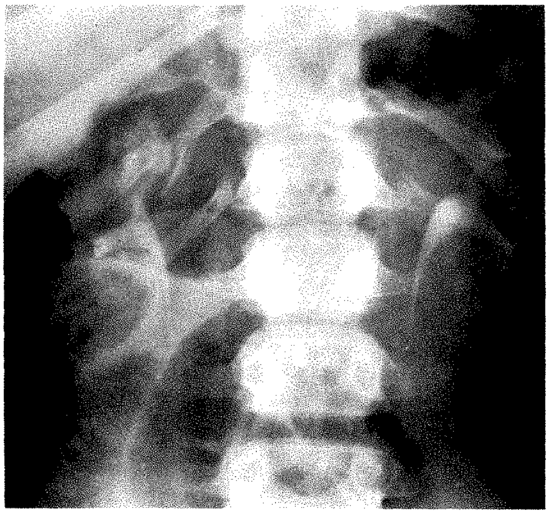
Fig. 5. Case 10. Male, aged 11 years 7 months. Excretory urogram for hematuria on day of injury. Extravasation of contrast material from superior calyx on right. Note rib fracture in area of extravasation.

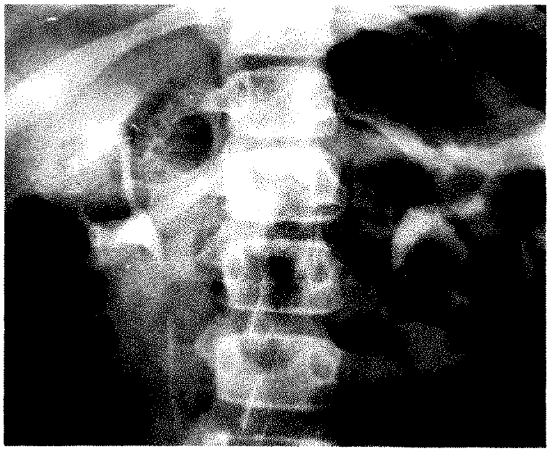
Fig. 6. Case 10. Excretory urogram 9 days after injury. No extravasation or residual deformity. Superior calyx on right is elongated.

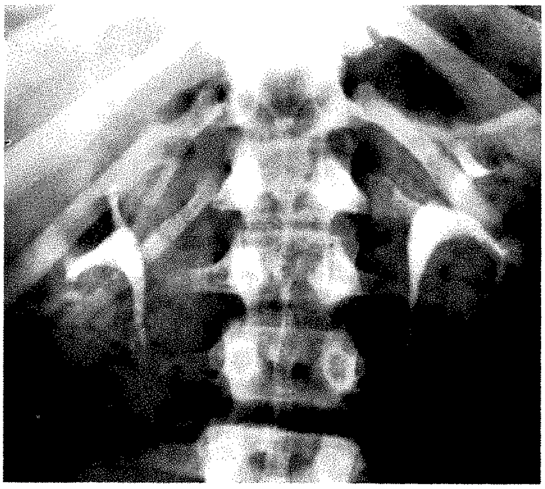
Fig. 7. Case 10. Excretory urogram 1½ years after injury. Superior calyx on right is now apparently shortened when compared to Figure 6, but otherwise normal.

the presence of the oxycel gauze and was the consequence of foreign body reaction rather than injury.[8]

In our Case 10, the injury was moderately severe as indicated by some extravasation of the contrast material into the renal parenchyma and the rib fractures. However, the sequels were mild roentgenologically as shown in the examination 19 months after the injury. In fact, hematoma around the upper pole of the kidney could have tilted it forward so that the full length of the superior infundibulum was projected onto the original roentgenogram. With resumption of its normal position after healing, the shortening observed could represent foreshortening by projection. The renal outline was insufficiently clear for identification of marginal changes.

The frequency of sequels in our series is not as high as that reported by DuChamp and his associates.[3] It is possible that this results from the failure to separate cases with mild injury from those with severe injury. Obviously, the extent of injury would play an important role in the end result, and in this regard, both of our cases with pathologic changes in the follow-up examination had moderate to severe injury to the kidneys. However, it is extremely difficult to equate severity of injury in individual patients. The localization of injury with respect to major vascular structures may play an important role in the subsequent development of renal atrophy, deformity and renal hypertension.

One might anticipate a higher frequency of renal change in renal injury occurring in children than in adults, because the kidney has not yet achieved its full growth. It has been suggested that "atrophy" is expressed more strongly in kidneys which are still growing than in those which have achieved their full size. The younger the patient at the time of injury, the longer the follow-up, the more chance there should be of demonstrating abnormalities. However, it is difficult to determine the proper length of follow-up. In view of the finding of definite changes in seriously injured kidneys within a few months of the injury, one may possibly assume that the absence of significant changes 1 to 2 years after the injury would carry a good prognosis. The subsequent development of renal hypertension may depend on features which cannot be demonstrated by changes in renal size or shape. This complication has not occurred sufficiently often to be noted in the literature; therefore, its delayed appearance is still largely hypothetical. The possibility that some adults with renal hypertension had renal injury as children is a consideration for evaluation notwithstanding the great interest in primary vascular causes for the hypertension. Childhood injury is easily forgotten, especially when there are no immediate clinical sequels. Prospective study of individuals who suffered renal injuries as children should help elucidate this question; retrospective questioning of hypertensive adults may also be useful but is probably less reliable.

CONCLUSION

We believe that our study confirms the fact that renal atrophy and distortion of the renal pelves can occur in children following renal injury, but the frequency does not appear to be as great as suggested by previous authors. The relationship of post-traumatic renal atrophy to the nature and severity of the injury is not clearly defined. Further long term studies will be necessary to determine the relationship, if any, to renal hypertension occurring in adult life. Meanwhile, a follow-up excretory urogram within 1 to 2 years after renal injury is warranted in order to identify any delayed anatomic sequels to the injury.

SUMMARY

Two of 14 children with clinical or roentgenographic evidence of renal injury demonstrated delayed deformity of calyceal systems, presumably due to atrophy of damaged renal tissue. No clinical manifestations have been associated with these changes. No significant relationship of

similar changes following renal injury to the subsequent development of renal hypertension was discovered in the available literature, but continued observation of affected individuals is recommended.

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STRIATED URETERS AND RENAL PELVES*

PRELIMINARY REPORT

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URINARY tract infections are among the most common illnesses of infants and children. Roentgenographic studies are essential in identifying areas of involvement whether they be obstructive or wholly on the basis of inflammatory change.

The purpose of this paper is to call attention to the urographic demonstration of striations of the ureters and renal pelves which, to our knowledge, have not been described before. The significance of these changes has not as yet been determined but we found them to be associated with inflammatory processes of the urinary tract.

ILLUSTRATIVE CASE

A 6½ year old girl was referred to the Los Angeles Children's Hospital with a history of recurrent urinary tract infections associated with chills and fever. She also had always been enuretic. No other complaints were elicited from the history. No abnormal findings were detected on physical examination. Analysis of the urine revealed no abnormalities other than 1–3 leukocytes per high power field. A culture of the urine was positive for *E. coli*.

On the intravenous urogram, linear striations were seen in the renal pelvis and uteter on the right; the left side was normal (Fig. 1, 2, and 3). Retrograde studies confirmed the findings in the left renal pelvis and ureter (Fig. 4) and also demonstrated similar changes in the slightly dilated right ureter. The cystogram revealed reflux on the right side but not on the left. The cystoscopist reported the bladder neck to be normal and no abnormality was observed on voiding cystourethrograms. Subsequent urograms, 6 months later, showed persistence of these findings on the right side; the left side remained normal.

DISCUSSION

According to Campbell,[1] infection may reach the ureter by the descending route from hematogenous renal infection from above, by the ascending route from direct urogenous reflux from the bladder, or by the ureteral and periureteral lymphatics. In mild ureteral infection, the inflammation is limited to the mucosa and submucosa, while severe infection involves deeper layers which heal by sclerosis. He also believes that many instances of hydronephrosis have been caused by inflammatory

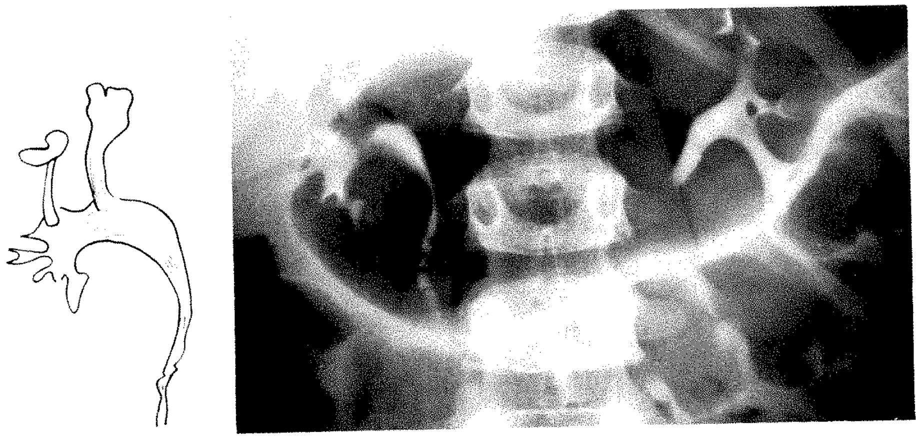

FIG. 1. Line drawing of right renal collecting structures and roentgenogram. The roentgenogram shows the linear, parallel striations on the right. The left side is normal.

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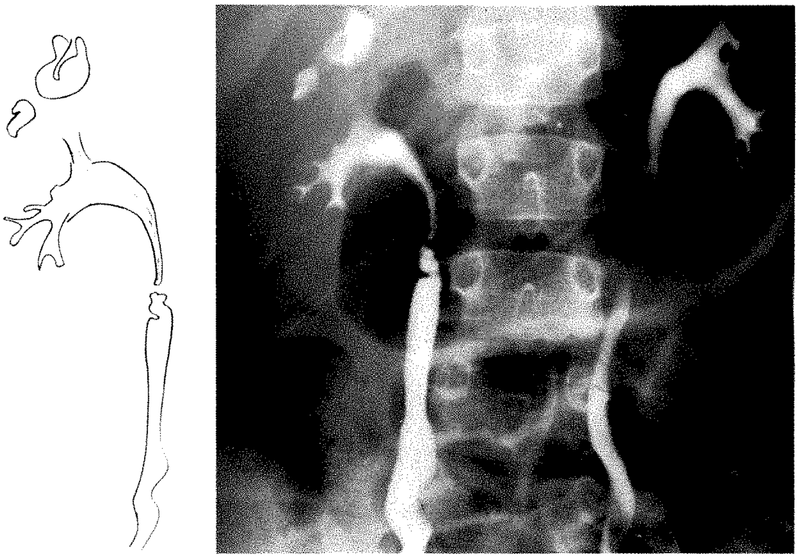

Fig. 2. Line drawing of right renal collecting structures and ureter and excretory urogram showing striations in the collecting structures and ureter on the right side.

ureteropelvic obstruction and these have been erroneously considered to be congenital.

Willams[4] states that it is generally conceded that urinary infection and ureteral inflammation may cause slight ureteral dilatation. He also states that urinary infection predisposes to ureteral reflux.

The striations, which are the subject of this report, are demonstrated both on excretory urograms and retrograde studies. They may be seen only in the renal pelvis or calyceal system (Fig. 3). On the other hand, they may be limited to the ureter (Fig. 4). Often all of these areas are involved. They consist of alternating, parallel, radiolucent and radiodense lines running in the long axis of the involved structure. On occasion, the striations are readily apparent on all of the studies, but, at times, they are quite subtle and have to be looked for carefully. The changes resemble rugae and might be likened to the normal mucosal pattern of the esophagus as seen when oral contrast medium is administered. Although it is conceded that this finding may indicate only an incompletely distended ureter which, at this particular point of enlargement, would show this pattern, it is more likely that it represents an exaggeration of the normal mucosal pattern of the ureter due to an inflammatory process. It does differ, however, from the rippling effect as noted by Garrett, Rhamy and Carr.[3]

During the past 4 years, we have noted the striations as described. Within the past 9 months, 19 patients had been seen who had striations demonstrated in the renal pelvis or ureter, or both, on urographic study. The illustrative case was chosen because of the minimal clinical and laboratory findings of urinary tract infection. All of the patients were sent to the Radiology Department for study because of symptoms and/or laboratory findings of fever, pyuria, frequency, urgency or dysuria. In our group with striations, there is a pre-

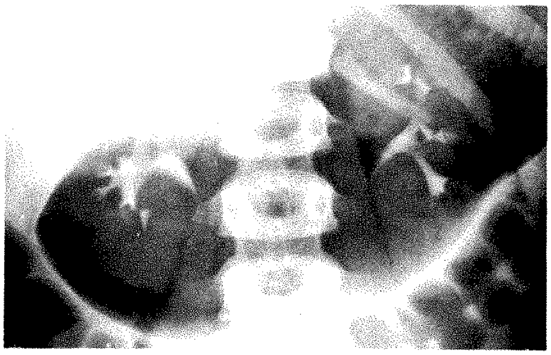

Fig. 3. Excretory urogram showing striations in the renal collecting structures.

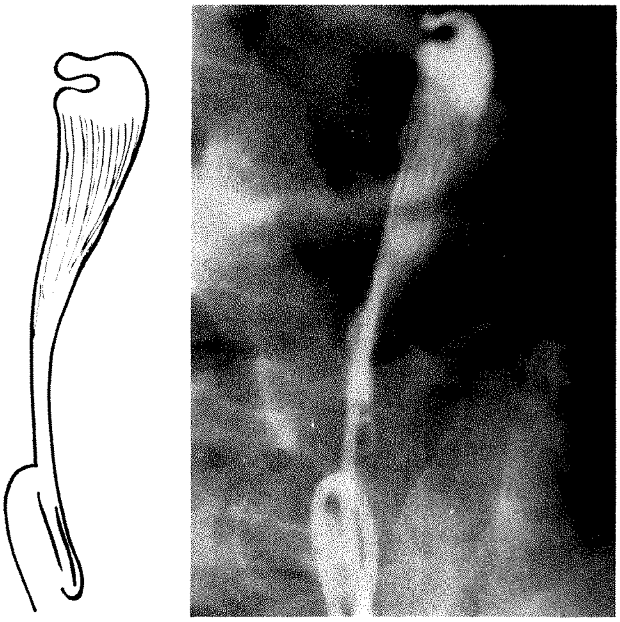

Fig. 4. Line drawing of a portion of the left ureter and retrograde pyelogram.

ponderance of girls to boys in a ratio of 3:1. Also, for some as yet unexplained reason, this phenomenon is observed more frequently on the left side than the right. It is of interest to note that in about 65 per cent of our cases, there has been ureteral reflux demonstrated on the cystourethrogram and usually on the striated side.

We have restudied a limited number of these patients who have been adequately treated for infection and have not been able to identify any striations on the repeated studies. No reflux was demonstrated by repeat cystourethrography.

DeLuca, Fisher and Swenson[2] reported on a review of 1,279 patients with urinary tract infections. Of this group, 1,079 had no underlying mechanical obstruction. They also pointed out the difficulty, at times, of establishment of the diagnosis and the appreciable delay in treating the infection. If the striated pattern is truly due to infection, then this would be an additional aid in making the diagnosis.

SUMMARY

1. A heretofore undescribed finding on urographic studies of infants and children is described.

2. This consists of alternating, linear, radiolucent and radiodense lines in the renal pelvis or ureter as observed on excretory urograms or retrograde pyelograms.

3. It is postulated that these changes are due to an inflammatory process while conceding that further study is necessary to determine their exact significance.

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"perichondrial" and "endochondral membrane bone." By such characterizations, the notion of "varieties of ossification" became established. As will be seen, all unify in a simple physiologic explanation.

2. Primary endochondral bone formation.

3. Some calcifying cartilaginous matrix persists as in marble bone disease (Fig. 6). This has been recorded as "intrachondral" bone. In adult sphenoid bones small areas of calcified cartilaginous matrix are often discoverable, especially in Caucasians. While persistence from fetal life is biologically improbable, it is evidence of pluripotency in adjacent cells and an activity long suspected to be a source of otosclerosis.

4. Appositional lamellar "periosteal membrane bone" greatly thickens the sphenoid (G—a wedge), not only on cranial surfaces as supposed. The interrupted microscopic maze of this layer at the fetal dural surface contrasts with the continuous "endosteal" bony labyrinth (Fig. 5).

Petrous bone is often considered unique with such distinctive histologic components. Several incongruous suppositions in pathogenesis have grown upon this foundation; for example:

Supposition A. "That membrane bone formation differs basically from endochondral bone, and has inferior powers of regeneration." This is often taught but does not stand up clinically. For instance, fractures of calvarium do heal by bone in children and usually by fibrous union in adults. Let us look at other membrane bones. The mandible is one, for Meckel's cartilage atrophies, and its fractures heal by ossification at all ages if immobilized. Fractures of facial bones heal similarly. Fractures of the sphenoid also heal by osteogenic response, *unless the bony labyrinth is fractured*, when fibrous union appears. This has been interpreted to mean that the "middle layer"[14] or "central endochondral bone"[22] has a very poor osteogenic response even in comparison with periosteal bone. It is invoked to explain why some operative labyrinthine fenestrae tend to remain open. These supposed layers are so scrambled microscopically that such views are untenable.

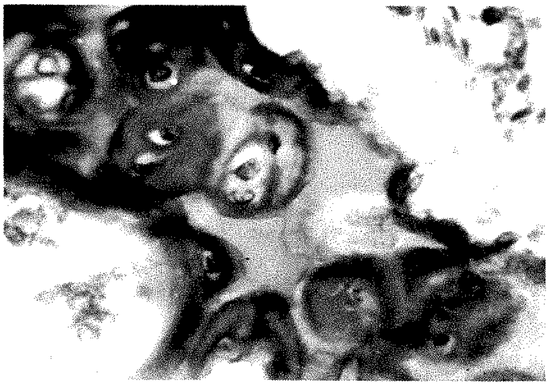

Fig. 6. Photomicrograph of a trabecula of the so-called "middle layer" of the petrosa. New nonlamellar woven bone encases and is itself encased by persisting hyaline cartilage.

Ham and Leeson[8] showed that osteoblastic cells of the membranous inner periosteum still retain the ability to differentiate into chondroblasts. They produce cartilage if capillaries are unable to keep up with their rapid reactive growth after fracture. In other words "membranous" or "endochondral bone formation" depended on provision of capillaries. For example, cartilage production in mid-shaft fractures of long bone is a commonplace component of "membrane bone" periosteal callus.

The cause of fibrous union in adult calvarial fractures remains unknown. The effect of cerebral pulsations has not been investigated as far as we are aware. Certainly cartilage does not appear in calvarial fractures. For cranial bony regeneration to occur in experimental animals, it is known that the presence of dura mater is essential.[25] In clinical observation cerebrospinal fluid, synovial fluid, or perilymph leaks seem to inhibit osteogenesis.

Supposition B. "That the continuous shell of the bony labyrinth differs from periosteal bone, which is histologically porous" (Fig. 5). Ham and Leeson[8] found that the majority of the osteocytes in bone are never more than a tenth of a millimeter from the nearest capillary. Presumably this is the functional limit of osmotic nutrition of bone which occurs through interlacunar canaliculi. This determines the maximum thickness of bone trabeculae everywhere, and the same capillary spacing is seen in compacta, which is but an example of completely contiguous trabeculation.

The intact rampart of "endosteal bone," which encloses canals and the cochlea, therefore, reflects only its uniform nutrition as a trabecula presumably from the enclosed circulating perilymph. Periosteal bone trabeculae are physiologically identical in thickness, but model their network of capillary grids.

Supposition C. "That the petrous bone is unique in retaining nonlamellar embryonic woven bone." Pritchard[19] has shown a similar minor admixture near cranial sutures, ligamentous attachments, and tooth sockets. Elsewhere, primary web-like woven bone is replaced, through remodelling during growth, by trabeculae now oriented along lines resisting mechanical stress. The petrous bone is unique only in reflecting that some of its primary mesh and appositional thickening are not modelled under the influence of gravity, growth, or muscle pull. Thus, no inner cancellous core of resorption develops. The interlocked rock-like mesh without linear orientation is in a random ply. The lack of haversian trabecular orientation is reflected in the unruly directions which fractures follow through the petrous bone.

The petrous bone is the only passenger bone in the body and adapted to other function. Such structure is admirably suited to sound conduction from nasal resonators through the zygoma and mandibular condyles by which we all constantly monitor and modulate our own projected voice intensities.

This nongravitational bone pattern is seen, for example, throughout the skeletal system of whales and seals. Their bones have no marrow cavities, with much cancellous woven bone and thin compacta. Such features remain as a functioning factor in the petrosal bones of the human race.

SUMMARY

In the fetus, the inner ear, tympanum and ossicles are the sole structures which reach adult size by mid-term. They are visible in roentgenographic relief especially clearly at 5 months, unobscured by petrous ossification. This bony labyrinthine shell of adult shape and size is most useful for developing familiarity and orientation needed for interpretation of petrosal disease.

In a survey of 20 pairs of labyrinths, remarkable similarity in size was noted. It is suggested that the cochlear end organ receptors have a mathematically predetermined size based on the frequencies they are to reproduce. Their development is thus not linked to the rate of body growth in general.

Various distinctive patterns of petrosal osteogenesis, long considered separate and unique, are shown to be very similar physiologically. Incongruous observations on osteogenesis in repair, inexplicable on former suppositions, are reviewed and linked with other factors. The petrosa appears to be a passenger bone, unmodified by gravity or muscle pull and admirably suited to sound conduction from nasal resonators by which we constantly monitor and modulate our own voice production.

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PANTOPAQUE VISUALIZATION OF A CONGENITAL DURAL DEFECT OF THE INTERNAL AUDITORY MEATUS CAUSING RHINORRHEA*

REPORT OF A CASE

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RECURRENT unexplained attacks of meningitis during childhood demand exhaustive search for a possible congenital communication of the subarachnoid space with the surface of the body. It is of utmost importance that such a communication be recognized and corrected to avoid the possibility of critical infection which may lead to fatality or irreversible central nervous system damage. The most common such anomaly is the persistent dermal sinus tract, whose external opening can ordinarily be recognized in or near the midline, particularly in the occipital or lumbosacral areas.[7]

Other anomalous communications may be indicated by the discovery of rhinorrhea or otorrhea. In the absence of skull fracture, recent surgical operation, or bone erosion by tumor, infection, arteriovenous malformation or hydrocephalus, these cerebrospinal fluid leaks point to localization of an abnormal communication from the subarachnoid space into the nasal cavity, paranasal air sinuses, nasopharynx, mastoid, or various parts of the inner or middle ear. Demonstration and correction of such cerebrospinal fluid fistulae have often proved most challenging and frustrating to the surgeon.

Because this is such a critical and frequently such a difficult problem, a recent unusual case is discussed in detail. The purpose of the authors is (1) to point out many of the common difficulties in locating the cause for recurrent meningitis, (2) to describe the use of an opaque medium (pantopaque) to visualize under the image intensifier the escape of cerebrospinal fluid from the pontine cistern into the middle ear and thence by way of the eustachian tube into the nasopharynx, and (3) to document another of the rare cases of otorrhea and rhinorrhea associated with a congenital defect of the petrous portion of the temporal bone in the region of the internal auditory meatus.

REPORT OF A CASE

S.F. (A46-10-72) was first admitted to the Children's Hospital Medical Center at 16 months of age on July 22, 1957. He was transferred from another hospital where he had been admitted 3 days previously because of fever, vomiting, stiffness of the body and cyanosis. Lumbar puncture at the time of admission to the referring hospital had shown 1,500 white blood cells per cu. mm. of which 90 per cent were polymorphonuclears. Cultures of the cerebrospinal fluid were sterile; nose and throat cultures grew *Micrococcus pyogenes* var. *aureus* and *pneumococci*. He had been treated with penicillin and sulfadiazine.

There were two previous admissions to the referring hospital, one at the age of 11 months and the other at the age of 14 months. At the time of his first hospital admission in February, 1957, pneumococcal meningitis was diagnosed by culture and smear of the cerebrospinal fluid and was treated with penicillin, sulfadiazine, and oxytetracycline. Within 24 hours the cerebrospinal fluid was reported as sterile. He had developed subdural effusions which cleared with repeated taps.

His second admission was in May, 1957 when he developed vomiting and a rigid neck after having had purulent coryza. He had also been found to have red, bulging tympanic membranes bilaterally. Cerebrospinal fluid cultures at that time also grew out *pneumococci*. He had again been treated with penicillin, sulfadiazine, and chloramphenicol intravenously. Again the cerebrospinal fluid was sterile within 24 hours. Skull roentgenograms were reported as negative for mastoid abnormality.

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Past medical history revealed that the child had been born without incident after an uncomplicated gestation. At 2 months of age he had fallen from the kitchen table, was not unconscious, and skull roentgenograms were reported as negative. He was sitting alone by 10 months, and pulled himself to a standing position by 11 months. He was not vocalizing at the time of his first Children's Hospital Medical Center admission. His mother felt certain that the child was deaf since he at no time had shown any reaction to noise.

His physical examination in July, 1957 showed an active child who made no response to sound. His head circumference was 44.5 cm., length 76 cm., weight 21 pounds. His fontanelle was 2 cm. wide and flat. Both tympanic membranes were dull and injected. The one on the right had a whitish gray exudate in the posterior superior quadrant. Neurologic examination, in addition to the deafness, revealed symmetrically brisk reflexes with extensor plantar responses. A careful search of the skin revealed a dimple in the sacral area which could be probed to within 1 cm. of the spinous process.

Lumbar puncture yielded sterile fluid with 660 white blood cells per cu. mm. of which 555 were polymorphonuclears. Three subsequent taps were also sterile; the last on July 26, 1957 showed no white blood cells. On July 29, 1957, the sacral dermal sinus tract was excised; it did not penetrate the fascia.

On August 6, 1957, the Ear, Nose and Throat Service performed an adenoidectomy and exploratory paracentesis of both tympanic membranes. The right ear was dry; the left yielded 0.5 ml. of serous fluid which grew out many *Micrococcus pyogenes* var. *aureus*. On August 8, 1957 the sacral wound separated and a persistent leak of serous fluid developed. On August 9, 1957, serous fluid was also noted to be draining from the left ear. On August 10, 1957, indigo carmine was injected into the lumbar theca to determine if the sacral wound was communicating with the subarachnoid space. The dye appeared in the ear canal; none in the sacral wound. Three days later, the child developed leakage of cerebrospinal fluid from the nose.

On August 17, 1957, a left temporal craniotomy and exploration of the petrous pyramid through the middle fossa were performed. No dural defect nor site of cerebrospinal fluid leakage could be found. For 5 days postoperatively, the child exhibited both rhinorrhea and otorrhea from the left ear. The otorrhea stopped on the fifth postoperative day. Indigo carmine was injected by lumbar puncture, and appeared in the left nostril 3 minutes later; it appeared in the left ear canal 8 hours later. On August 27, 1957, myelography was unsuccessfully attempted. By September 1, 1957, no otorrhea nor rhinorrhea could be detected after holding the patient inverted for 3 minutes.

Roentgenograms of the skull reportedly showed no abnormalities of the cranium or paranasal sinuses, although the left mastoid was described as of greater density than the right. No spine defects were noted.

After discharge, the child was followed in the Out-Patient Clinic, where a hearing loss of 90–110 decibels was recorded in both ears by psychogalvanic audiometry. The parents reported no leakage until October, 1958, when they noted a watery rhinorrhea. At this time, however, it could not be demonstated even with the child inverted by the examiner.

In January, 1959 the child was hospitalized at another hospital, again with pneumococcal meningitis. He was next seen in the Ear, Nose and Throat Clinic in mid-February, 1959 where his examination was reported as normal. In April, 1959 the parents reported that the child was having frequent bouts of watery rhinorrhea. Hearing tests at that time again showed a 90–100 decibel loss in both ears.

In July, 1959 at the age of 3 years and 4 months, the child was again admitted to the referring hospital where he was started on penicillin after a diagnosis of pneumococcal meningitis was made by smear and culture. Examination on admission showed no otorrhea nor rhinorrhea. The left external ear canal was filled with purulent exudate; paracentesis yielded thick mucous fluid which was sterile on culture. Lumbar puncture showed cloudy fluid with 8,900 polymorphonuclear cells per cu. mm. The smear of the cerebrospinal fluid showed encapsulated gram-positive diplococci which did not grow on culture.

Roentgenograms of the skull revealed the craniotomy defect. The mastoid on the left was described as "underdeveloped with increased density throughout, with loss of clarity of all landmarks." In the Hertz projection there was a defect in the left temporal bone with sclerosis of the mastoid. There was no destruction of the petrous tip nor of the body of the petron.

After a course of intravenous penicillin and chloramphenicol, the child was discharged without oto- or rhinorrhea.

The third Children's Hospital Medical Center admission of this patient was on December 29, 1959. Since his discharge, he had been admitted to the referring hospital 5 times with pneumococcal meningitis; the last admission being 5 days prior to transfer. Lumbar puncture yielded cloudy fluid with 10,000 polymorphonuclear cells. He was again treated with penicillin and chloramphenicol.

On January 4, 1960, pantopaque was introduced into the cisterna magna under fluoroscopic control after previous lumbar myelography had been unsuccessful. At that time no external communication could be demonstrated. In subsequent roentgenograms, one of us (M.H.W.) noted "2 droplets of pantopaque" in the petrous bone, just lateral and superior to the auditory meatus and suspected that the opening might be posterior rather than anterior.

On January 22, 1960, the left petrous pyramid was re-explored through the middle fossa and the tentorium was sectioned, but no dural defect was found (D.D.M.). All nerves and vessels were wrapped in gelfoam at their foramina. The patient's postoperative course was uneventful. He was discharged on January 30, 1960, without any leakage. Following discharge, he was seen in the Out-Patient Department on two occasions, still with complaints of rhinorrhea, but on neither occasion could the leak be demonstrated.

On March 5, 1960, the patient was re-admitted to the Children's Hospital Medical Center for the fourth time with a history of fever, vomiting, headache and left-sided rhinorrhea. Except for meningeal irritation, deafness, and rhinorrhea, the physical examination was normal. A lumbar puncture showed 750 white blood cells per cu. mm; he was started on penicillin and chloramphenicol. The culture subsequently was reported as sterile. On March 11, 1960, a left frontal craniotomy and exploration of the cribriform plate were performed and a fascial graft inserted (D.D.M.). His postoperative course was uneventful and he was discharged on March 18, 1960 with no sign of rhinorrhea. The parents returned the child to the Out-Patient Department on March 23, 1960 with a history of rhinorrhea starting the first day after discharge. Plans for an elective admission were subsequently cancelled because the rhinorrhea stopped. He was seen again on April 6, 1960 for a follow-up visit at which time the parents reported no leak.

His fifth admission was from April 15, 1960 to April 23, 1960. He entered with fever (103°F.), vomiting and headache. No leak could be demonstrated during his hospital stay. Cerebrospinal fluid contained 6,000 polymorphonuclear cells per cu. mm.; cultures revealed *alpha streptococci*. Roentgenograms of the skull showed residual contrast material in the basilar cisterns but none in the petrous bone.

On May 11, 1960, the child was re-admitted because of persistent rhinorrhea which developed again shortly after discharge. At this time there was no suggestion of otorrhea so a bifrontal craniotomy was performed to expose both cribriform plates, the sphenoid and sellar region (D.D.M.). The only possible site of leak was again an outpouching of the dura through one of the holes of the cribriform plate. This was sealed with muscle and gelfoam and was covered with a periosteal graft. On the second postoperative day, the patient developed profuse rhinorrhea from the left nostril with fever and signs of meningitis. Culture of the cerebrospinal fluid revealed *pneumococci*. He was treated with intravenous penicillin and chloramphenicol.

Under general anesthesia, a lumbar puncture was performed and 1 ml. of buffered phenolsulfonphthalein was injected. An Ear Nose and Throat consultant then performed selective packing of the nasopharynx and choanae. It was his opinion that the dye was not coming from either eustachian tube; he felt the most likely site was from the ostium of the sphenoid sinus. On June 8, 1960, pantopaque was again introduced into the cisterna magna. Fluoroscopy and follow-up roentgenograms failed to demonstrate any fistulae. No further surgery was offered and the patient was discharged only to return 1 day later with fever, vomiting, headache, and rhinorrhea. In addition to positive Kernig and Brudzinski signs, the patient also had 5,000 polymorphonuclear cells per cu. mm. in his cerebrospinal fluid. Cultures were subsequently reported as yielding no growth. He again responded well to penicillin and chloramphenicol. On June 20, 1960, the bifrontal craniotomy was reopened (D.D.M.). After thorough negative exploration including the pituitary fossa, the cribriform plate was again packed with muscle. There was no sign of leak at the time of operation. The postoperative course was remarkable this time only for the lack of rhinorrhea. The patient was discharged on the tenth postoperative day with no sign of leak.

The patient did well until August 4, 1960, when he returned with lethargy, fever, vomiting, headache, and stiff neck. His physical findings were as before. Lumbar puncture revealed 220 white blood cells per cu. mm.; smear showed gram-positive cocci in chains, which the cultures showed to be *gamma streptococci*. Treatment again consisted of penicillin and chloramphenicol intravenously. Following intrathecal administration of phenolsulfonphthalein, the dye was noted on the sheets the following morning; none having appeared during the few hours of close observation. On August 23, 1960, another pantopaque study was performed under fluoroscopy. The survey skull roentgenograms suggested that 2 minute droplets of residual pantopaque from the previous contrast study were trapped in the left petrous bone in the region of the middle ear. Consequently, another attempt at demonstrating the cerebrospinal fluid leak by roentgenography with contrast medium was carried out, directed to this area. Three cubic centimeters of pantopaque were injected into the subarachnoid space via the lumbar route. The radiopaque medium was monitored by direct viewing through a fluoroscopic image intensification system and movement of the pantopaque by gravity was controlled by shifting the patient's position as in conventional myelography. The contrast medium was kept in one unbroken column, run down the spinal canal, through the foramen magnum, up the clivus, and then pooled in the left lateral recess of the cisterna pontis. Shortly thereafter, the fluoroscopist noted droplets of the medium on the back of the patient's tongue. While keeping the contrast medium pooled in the left cerebellopontine angle, the patient's head was positioned for roentgenography in the submentovertical view of the skull and the contrast medium could be observed in the left middle ear and posterior pharynx. Spot roentgenograms taken in this position (Fig. 1, *A* and *B*) showed opacification by pantopaque of the left middle ear, left eustachian tube and droplets appearing on the posterior pharyngeal wall at the site of the eustachian tube orifice. Although the exact site of entry of the medium into the middle ear was not identified, its course from the posterior fossa, through the middle ear, eustachian tube and into the nasopharynx was established.

Accordingly, on September 2, 1960, suboccipital craniectomy with exploration of the left cerebellopontine angle was carried out. A dural defect projecting into a large bone opening at the internal auditory meatus posterior and inferior to the eighth nerve was noted by the surgeon (J.S.). The bone opening was filled with a mixture of bone wax and cotton in hope of promoting a fibrous reaction. Postoperatively, there was a temporary left facial weakness which improved rapidly. No cerebral spinal fluid leak could be demonstrated. On September 10, 1960 and again on September 12, 1960, intrathecal phenolsulfonphthalein was introduced but no evidence of rhinorrhea or otorrhea could be found. On September 14, 1960, the patient was discharged. He has been followed closely in the Out-Patient Department. At no time in the 2 years and 10 months since operation has any sign of rhinorrhea or otorrhea developed and there has been no recurrence of meningitis. He is presently attending a school for deaf children and is a bright, alert, attractive child. Physical examination except for his congenital deafness is normal.

DISCUSSION

In commenting upon the spontaneous cessation of otorrhea caused by basal skull fracture, Dandy[3] remarks " . . . this is fortunate because it would be difficult to determine the site of the fistula; *i.e.*, whether it was in the middle or the posterior fossa." Many neurosurgeons can confirm this difficulty. By using intrathecal phenolsulfonphthalein, indigo carmine, 5 per cent fluorescein[6] or radioactive Na^{24} [2] coupled with nasopharyngoscopic examination, it is usually possible to tell whether rhinorrhea is due to a local fistula through the cribriform

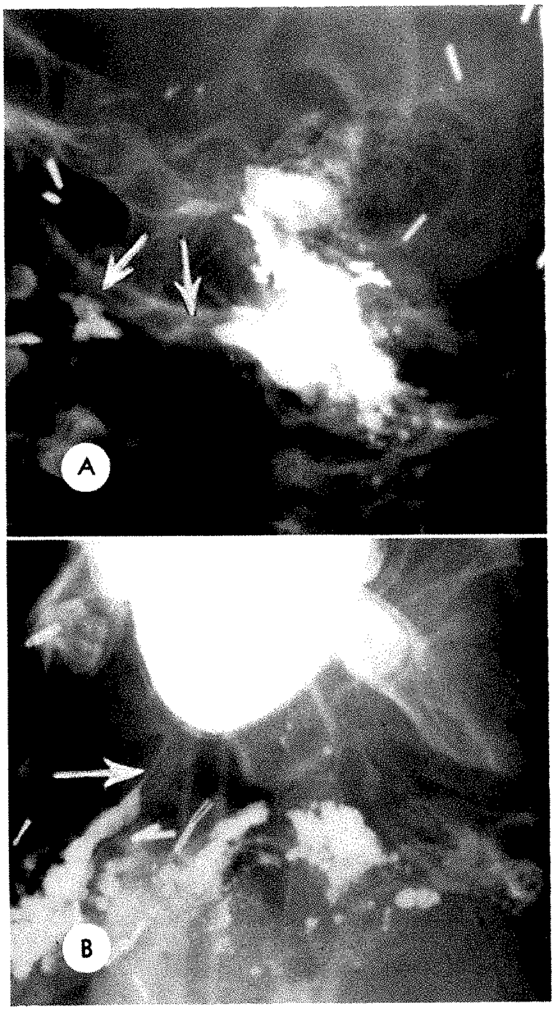

FIG. 1. (*A*) Lateral spot roentgenogram. Pantopaque is shown in cisterna pontis and middle ear. Note also (arrows) pantopaque entering ectatic bone portion of eustachian tube and in nasopharynx. (*B*) Submentovertex spot roentgenogram. Note pantopaque in dilated bone portion of eustachian tube, tapering to narrow column in normal-sized membranous portion on left side (arrow).

plate or paranasal sinuses, or whether the cerebrospinal fluid gets to the nasopharynx through one of the eustachian tubes. If indeed it can be determined to come by way of the eustachian tube, it still remains to locate the site of egress from the subarachnoid space. Even if it is apparent by roentgenographic examination that a congenital anomaly of the petrous portion of the temporal bone is present, no assumption regarding the exact location of the cerebrospinal fluid fistula is justified because the leak might still be from either the posterior fossa or the middle fossa.

Alberti and Dawes[1] have reported an incidence of congenital dehiscences of the tegmen tympani of 5.4 per cent in autopsied cases. Menzelius[8] and Ferrer[4] have described leaks occurring through defects at the internal auditory meatus. Updegraff[11] also described a congenital defect causing otorrhea which probably had its origin at the internal auditory meatus. Nulsen[9] and colleagues recently observed 4 cases of cerebrospinal fluid fistulae visualized by pantopaque in the subarachnoid spaces and 1 of these was a communication at the internal auditory meatus.

Accurate visual demonstration of the location of a cerebrospinal fluid fistula is possible by the use of pantopaque roentgen examination. In 1956, Ghouralal, Myers and Campbell[5] reported using pantopaque to demonstrate the origin of a cranio-otic fistula which developed following skull fracture. Their roentgenograms, taken after instillation of pantopaque into the cisterna magna, showed the opaque medium in the posterior fossa and in the nasopharynx; none was seen in the middle fossa. Raaf[10] has also noted the use of pantopaque to demonstrate the source of a cerebrospinal fluid fistula.

By allowing the persistent findings of rhinorrhea and meningitis to obscure the significance of the underlying and long established diagnosis of congenital deafness in the case reported here and having been lulled into a false sense of security by the cessation of otorrhea following the operations on the petrous bone, the attending surgeons mistakenly turned their attention to the cribriform plate and the paranasal sinuses as the source of the cerebrospinal fluid leak. It appeared that the otorrhea had been cured by the operation on the petrous pyramid. When the child re-entered with only rhinorrhea and no sign of otorrhea approximately 1 year after his first operation, an attempt was made to visual-

FIG. 2. Towne view. Cushing clips from previous operation on left side. Arrow points to anomalous inner ear structure. Note haziness of mastoid cells on left due to accumulation of cerebrospinal fluid.

ize the site of the leak with intrathecal pantopaque. Although the leak was not demonstrated, follow-up roentgenograms showed some pantopaque in the petrous portion of the temporal bone. On this basis, the petrous pyramid was again explored and the tentorium sectioned. Almost a year elapsed before the child returned again with rhinorrhea and still no evidence of otorrhea. Dural extensions into the cribriform plate were found and obliterated but this did not affect the rhinorrhea.

One of us (M. H. W.) had expressed the opinion that the origin of the rhinorrhea was from the posterior fossa. Nasopharyngoscopic examination after intrathecal phenolsulfonphthalein administration failed to demonstrate the dye coming from the eustachian tube, thereby leading to further exploration of the cribriform plate and sphenoid bone. When rhinorrhea again recurred following the anterior and middle fossa explorations, it was decided that the origin of the leak must be demonstrated before any further surgery was undertaken. After introducing 3 cc. of pantopaque into the lumbar theca with the patient under general anesthesia, the fluoroscopist (M. H. W.) was able to obtain the roentgenograms shown in Figure 1, *A* and *B*. Although the exact site of entry of the pantopaque into the middle ear could not be visualized, it was apparent that the opaque medium had entered the ear from the lateral recess of the pontine cistern. Figure 1, *A* and *B* shows pantopaque in the subarachnoid space, middle ear, ectatic bony portion and normal-sized membranous portion of the eustachian tube, and in the nasopharynx.

With the presenting problem of meningitis and cerebrospinal fluid leakage finally solved, attention was subsequently directed to the cause of the boy's bilateral deafness. Dr. A. S. MacMillan, Jr., roentgenologist at the Massachusetts Eye and Ear Infirmary reviewed this patient's roentgenograms with us and feels that the cochlea is absent on both sides and that there is a gross deformity of the vestibule on the left (Fig. 2). Therefore, this case appears to be similar to that presented by Menzelius[8] of a congenital dural defect at the internal auditory meatus associated with aplasia of the inner ear.

SUMMARY

An unusual case of intermittent otorrhea and rhinorrhea with recurrent meningitis due to a congenital fistula between the lateral recess of the pontine cistern and the middle ear is described.

After multiple abortive surgical explorations of the cribriform and petrous areas, the site of the anomalous communication was visualized in the region of the internal auditory meatus by pantopaque in the subarachnoid space under fluoroscopic examination. This led to proper operative correction through the posterior fossa. Another instance of otorrhea and rhinorrhea associated with congenital deafness is documented.

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AIR-PANTOPAQUE VENTRICULOGRAPHY IN CONGENITAL HYDROCEPHALUS AND MYELOMENINGOCELE*

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THE use of opaque contrast media in ventriculography has been documented in the literature.[1,2,3,5,7,8,10] In some institutions, pantopaque studies are being used routinely in selective cases to supplement or even sometimes in preference to air studies.[3,5,8,10] Its use, however, has been mainly limited to adults with tumors of the posterior fossa.

In the present study, similar principles, criteria and methods were applied in hydrocephalic infants in an effort to accurately demonstrate the exact location and nature of the pathologic process that interferes with the normal flow of the cerebrospinal fluid and in infants with myelomeningocele to detect unmanifested hydrocephalus due to other concealed anomalies. The conventional air studies have not always given satisfactory information as to the cause of hydrocephalus and location of the obstruction, and many times the diagnosis is based on indirect evidence with many insufficient and presumptive elements. It is the purpose of this communication to present and discuss a diagnostic method by which (1) the patency of the cerebrospinal fluid pathways can be easily demonstrated, (2) the presence of anomalies along its course can be accurately visualized, and (3) the extent of hydrocephalus can be readily estimated. Thus, it may contribute to an earlier and better evaluation in the treatment and prognosis of hydrocephalus and meningocele.

CLINICAL MATERIAL

Fifteen infants were included in the present series. They were divided into two groups. Nine showed clinical signs of hydrocephalus with increased head circumference, vomiting, bulging fontanels, separation of the sutures, and irritability. They had pantopaque ventriculography as part of a thorough neurologic investigation. The other 6 were infants with lumbar myelomeningocele and marked neurologic deficit of the lower extremities. None of them showed clinical evidence of hydrocephalus. They had normal head circumferences, soft anterior fontanel and no separation of the sutures. Ventricular contrast studies were done on all of them in an effort to determine the presence of other developmental anomalies along the cerebrospinal fluid pathways that might produce a disturbance in its circulation resulting in early or late appearance of hydrocephalus.

METHOD

With the infant in prone position, through the anterior fontanel, the right lateral ventricle is punctured and 10–15 cc. of air is injected in exchange to ventricular fluid. After the introduction of air, 1 cc. of pantopaque is injected into the ventricle. With the head in brow-down position, the oil is collected in the right frontal horn and the air occupies the uppermost part of the right occipital horn. Anteroposterior and lateral roentgenograms of the skull are taken at this stage. The contrast medium is then moved with the following manipulations:

1. By extending the head with the baby kept in prone position and then bringing the head back to the brow-down position, a good part of the pantopaque flows through the foramen of Monro to the optic recess of the third ventricle. At the same time during

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the manipulation, part of the air goes to the left ventricle so that at the end of this manipulation both occipital horns are outlined by air. The head is extended until the orbitomeatal line is parallel to the roentgenographic table and kept in that position for approximately 1 minute because of slow flow of the opaque material (Fig. 1, *A*, *B* and *C*).

2. The patient is then turned to the supine position with the head kept in extension. A good part of the pantopaque is collected in the suprapineal recess of the third ventricle, while the air outlines both frontal horns (Fig. 1 *D*).

3. By flexing the head to different degrees with the patient in supine position, the pantopaque flows through the aqueduct to the fourth ventricle, and finally to the subarachnoid space and the spinal canal (Fig. 1 *E*).

RESULTS

In the 9 hydrocephalic patients, the site of obstruction was accurately demonstrated. Aqueductal stenosis was found in 3 patients (Fig. 3, *A*, *B* and *C*; and 4, *A–D*). In 3 patients, the obstruction was demonstrated at the level of the foramina of the fourth ventricle (Fig. 2, *A*, *B* and *C*). Two showed block at the craniocervical junction (Fig. 5, *A*, *B* and *C*). One infant showed no evidence of block and the diagnosis of communicating hydrocephalus was established. In 5 cases the roentgenologic diagnosis was later confirmed at necropsy (Table I).

In the group of 6 infants with myelomeningocele, 2 had aqueductal stenosis (Fig. 6, *A* and *B*). One was obstructed at the foramina of the fourth ventricle and 1 at the craniocervical junction (Fig. 7, *A* and *B*). At the time of the roentgenologic evaluation, none of these 4 cases showed clinical evidence of intracranial pathology. In the other 2 patients, the air-pantopaque ventriculogram was normal (Table II). The clinical course in this group showed close correlation with the ventriculographic findings. One of the patients with atresia of the aqueduct started developing clinical signs of hydrocephalus at the age of 3 months and expired at the age of 8 months. Autopsy confirmed the diagnosis of aqueductal stenosis. In 1 of the other 3 patients with defective cerebrospinal fluid pathways, hydrocephalus became obvious at the age of 6 months. One had a shunt procedure at the age of 4 months when early signs of hydrocephalus appeared and further progression was arrested. The third patient was studied recently and is still under observation.

The 2 infants who showed normal ventriculograms have been followed for 5 and 16 months, respectively, without any clinical signs of hydrocephalus after surgi-

TABLE I

AIR-PANTOPAQUE VENTRICULOGRAPHY IN 9 CASES OF CONGENITAL HYDROCEPHALUS

Case No.	Age	Clinical Hydrocephalus	Ventriculographic Findings
1	12 mo.	Present	Atresia of foramina of Luschka and Magendie (Fig. 2, *A*, *B* and *C*)
2	3 da.	Present	Aqueductal stenosis (Fig. 3, *A*, *B* and *C*)
3	16 mo.	Present	Atresia of foramina of Luschka and Magendie
4	3 wk.	Present	Aqueductal stenosis (Fig. 4, *A–D*)
5	3 wk.	Present	Block at craniocervical junction
6	6 mo.	Present	Block at craniocervical junction
7	4 wk.	Present	Atresia of foramina of Luschka and Magendie
8	6 wk.	Present	Stenosis of aqueduct
9	4 mo.	Present	No block along cerebrospinal fluid pathway; communicating hydrocephalus

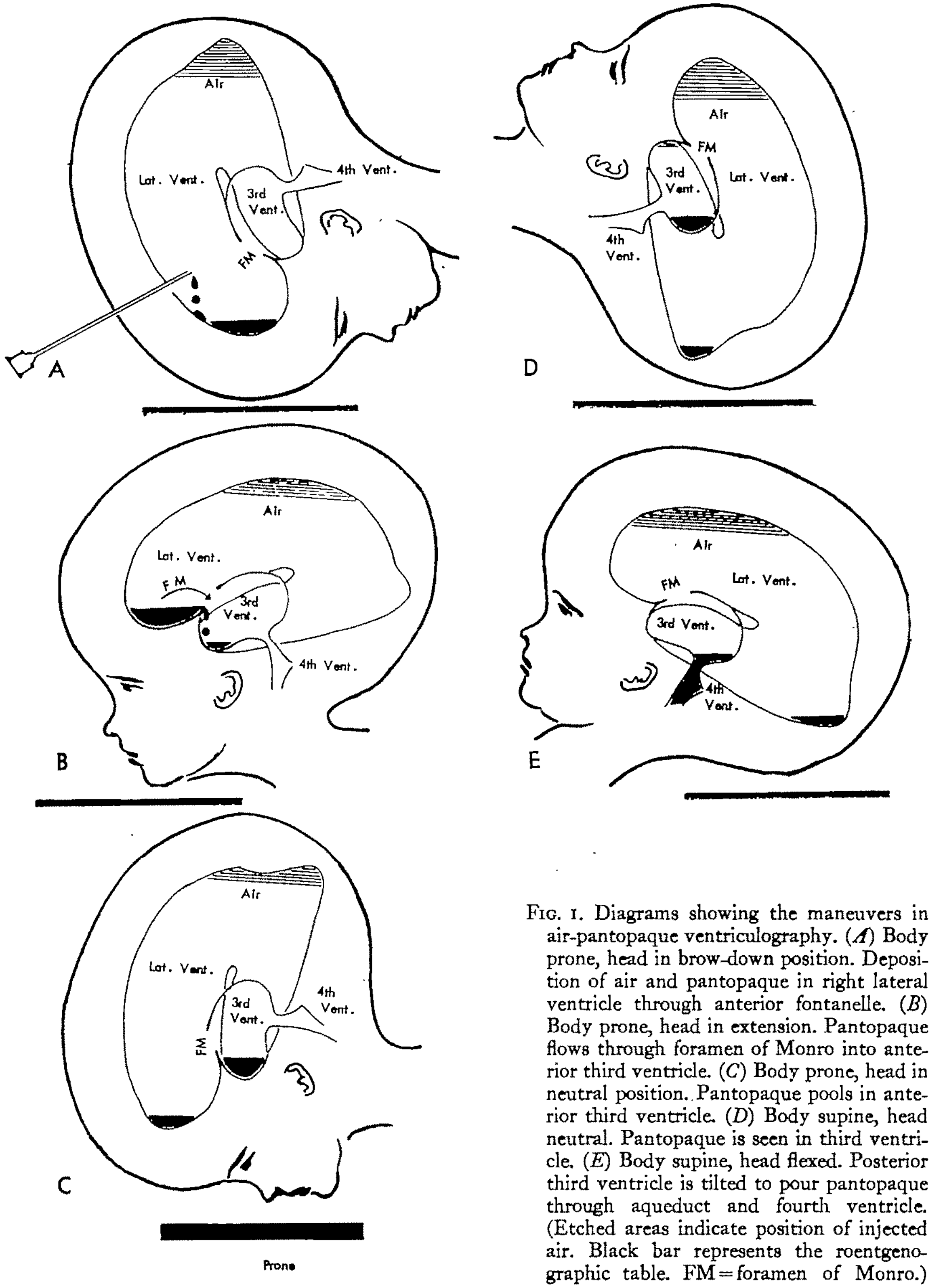


Fig. 1. Diagrams showing the maneuvers in air-pantopaque ventriculography. (*A*) Body prone, head in brow-down position. Deposition of air and pantopaque in right lateral ventricle through anterior fontanelle. (*B*) Body prone, head in extension. Pantopaque flows through foramen of Monro into anterior third ventricle. (*C*) Body prone, head in neutral position. Pantopaque pools in anterior third ventricle. (*D*) Body supine, head neutral. Pantopaque is seen in third ventricle. (*E*) Body supine, head flexed. Posterior third ventricle is tilted to pour pantopaque through aqueduct and fourth ventricle. (Etched areas indicate position of injected air. Black bar represents the roentgenographic table. FM = foramen of Monro.)

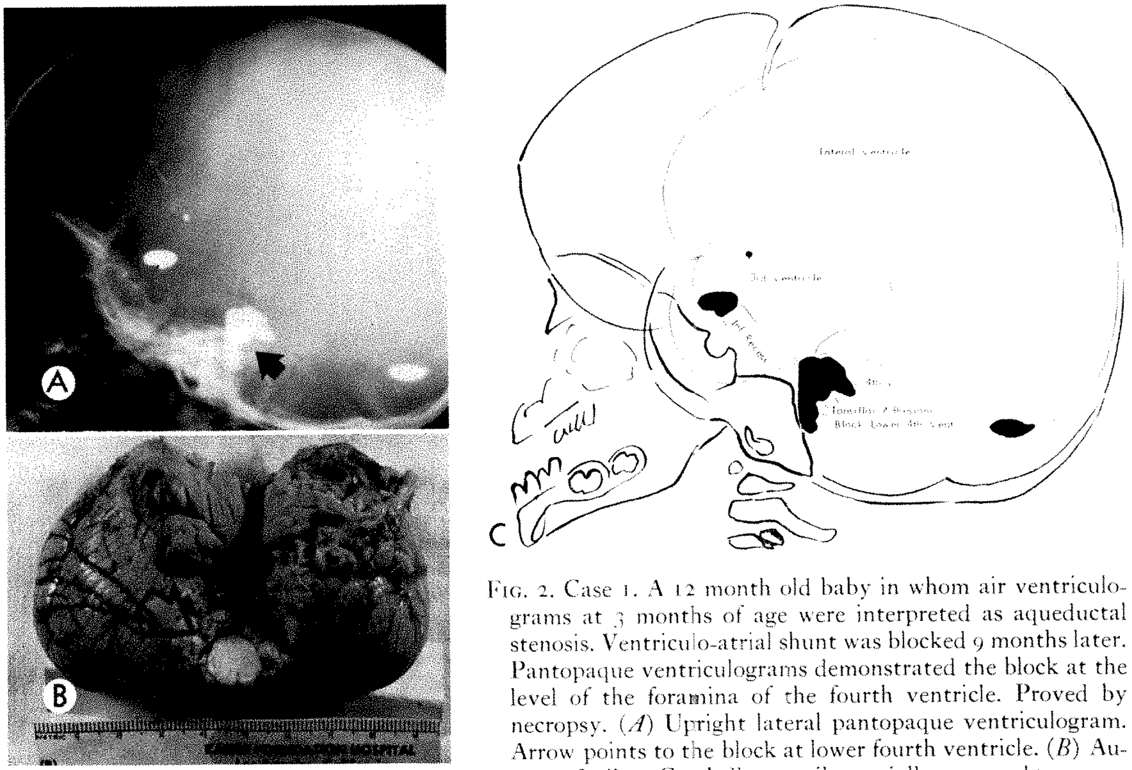


Fig. 2. Case 1. A 12 month old baby in whom air ventriculograms at 3 months of age were interpreted as aqueductal stenosis. Ventriculo-atrial shunt was blocked 9 months later. Pantopaque ventriculograms demonstrated the block at the level of the foramina of the fourth ventricle. Proved by necropsy. (*A*) Upright lateral pantopaque ventriculogram. Arrow points to the block at lower fourth ventricle. (*B*) Autopsy finding. Cerebellar tonsils partially removed to expose the block caused by adhesions which sealed the tonsils to the medulla oblongata (arrow) and absence of the ventricular foramina. Infolded cerebellar tonsils formed the serrated intraventricular defect. (*C*) Diagram of *A*.

cal repair of the meningocele.

In 11 of the 15 patients of this series, pantopaque ventriculography was performed in the first 6 weeks of life. All 15 patients tolerated the procedure well and there has been no untoward reaction. Careful follow-up showed no progression of their symptomatology or development of any neurologic manifestations which could be related to the intraventricular deposition of pantopaque.

DISCUSSION

In hydrocephalus, air ventriculography is often inadequate for the visualization of the cerebrospinal fluid pathways in the posterior fossa.[4,6,9] In most instances, the injected air is trapped in the highly dilated lateral ventricles without filling or with an inadequate amount of air in the posterior pathways in spite of repeated, extensive manipulations of the infant. On other occasions, when the posterior fossa structures are filled with air, interpretation of the study and analysis of the findings may be complicated by superimposed air shadows with lack of detailed outline of the individual structures.

Pneumoencephalography often fails to fill the cerebrospinal fluid pathways in the presence of posterior fossa pathology—especially with defects in the craniocervical function. Furthermore, it cannot be used in myelomeningocele.

The cisternal route should be excluded since a malformation at the region of the cisterna magna may be present and, therefore, may create major technical difficulties and hazards for the patient.

In our series, we combined the introduction of pantopaque with a small amount of air. The combination of the two media with an opposite weight relation to the cerebrospinal fluid permits full evaluation of the

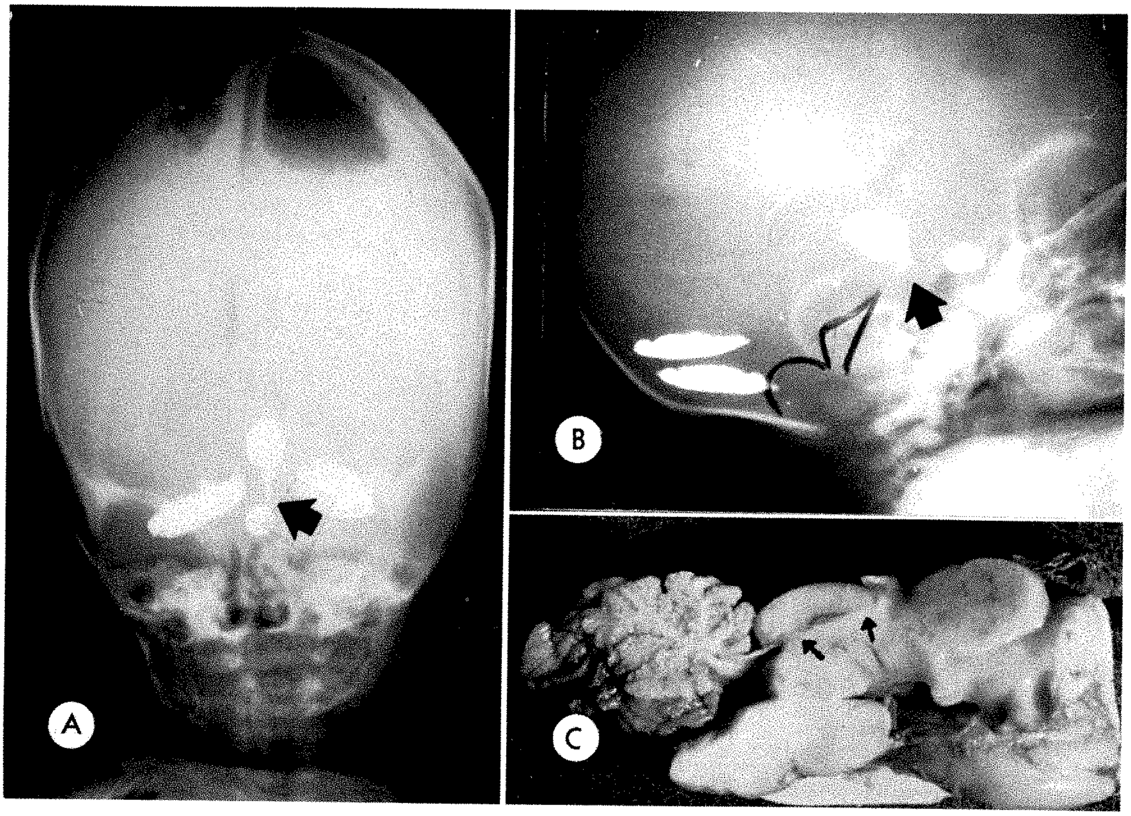


FIG. 3. Case 2. Air-pantopaque ventriculograms of a 3 week old hydrocephalic baby demonstrate aqueductal stenosis. Proved by necropsy. (*A*) Upright anteroposterior ventriculogram. Air outlines extent of hydrocephalus. Aqueductal stenosis is indicated by arrow. (*B*) Upright lateral ventriculogram shows the position of the fourth ventricle (block outline) and a dilated cisterna magna as seen at autopsy. (*C*) Sagittal section of brain stem, cerebellum and diencephalon. Hypoplasia of right cerebellum (dilated cisterna magna). Stenosis of aqueduct is indicated by arrows.

ventricular system with a minimum of manipulations by the spontaneous filling of opposite parts of the ventricles, pantopaque at one end and air at the other. Thus, the bubble air provides information on the presence and extent of hydrocephalus and at the same time the pantopaque outlines a malformation along the central pathway

TABLE II

AIR-PANTOPAQUE VENTRICULOGRAPHY IN 6 CASES OF MYELOMENINGOCELE

Case No.	Age	Clinical Hydrocephalus	Roentgenologic Hydrocephalus	Ventriculographic Findings
10	2 wk.	Absent	Present	Aqueductal stenosis (Fig. 6, *A* and *B*)
11	11 da.	Absent	Present	Atresia of foramina of Luschka and Magendie
12	3 wk.	Absent	Present	Incomplete block at craniocervical junction; possible Arnold-Chiari's formation (Fig. 7, *A* and *B*)
13	10 da.	Absent	Absent	Normal
14	2 wk.	Absent	Present	Aqueductal stenosis
15	7 da.	Absent	Absent	Normal

of the cerebrospinal fluid. With the use of 1 cc. of pantopaque and a few simple maneuvers, the pathways of the posterior fossa can be clearly visualized. The pantopaque sharply outlines the anatomic structures. It permits the demonstration of the size and shape of the aqueduct and pinpoints the site of obstruction. The fourth ventricle can be clearly delineated; the presence of the opaque substance in the subarachnoid

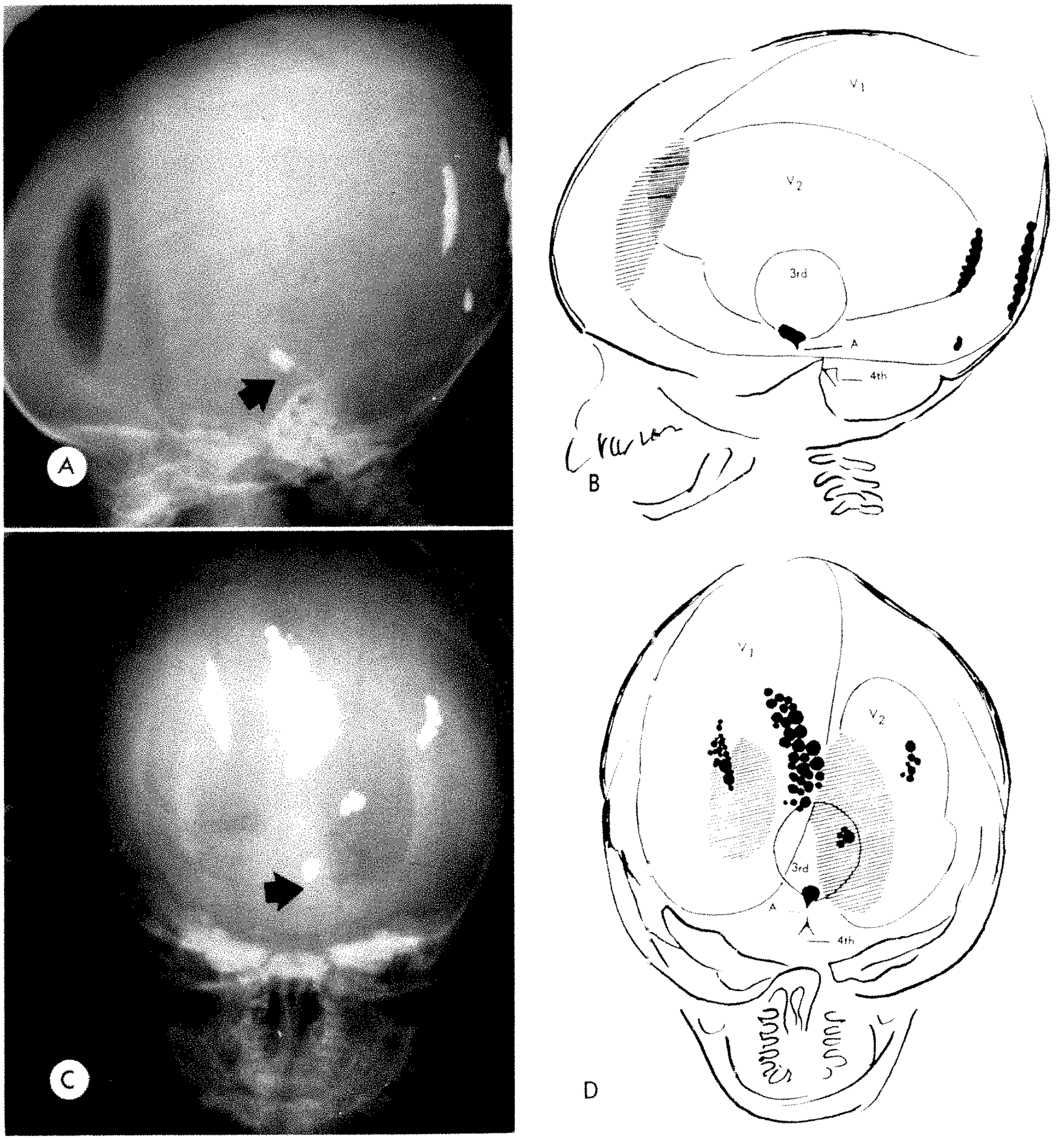
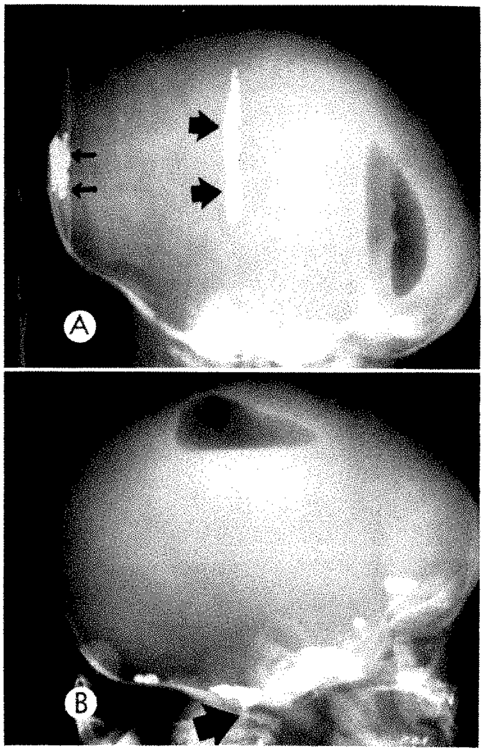


Fig. 4. Case 4. Air-pantopaque ventriculograms of a 3 week old hydrocephalic baby. Hydrocephalus was due to aqueductal stenosis. (*A*) Brow-up, lateral ventriculogram. Air and pantopaque in lateral ventricles indicate the extent of hydrocephalus. Arrow points to stenotic aqueduct. (*B*) Diagram of *A*. (*C*) Anteroposterior ventriculogram shows blocked aqueduct (arrow). (*D*) Diagram of *C*. V_1 and V_2 = right and left lateral ventricle; A = aqueduct. (Etched areas indicate injected air in lateral ventricles; black areas indicate pantopaque.)



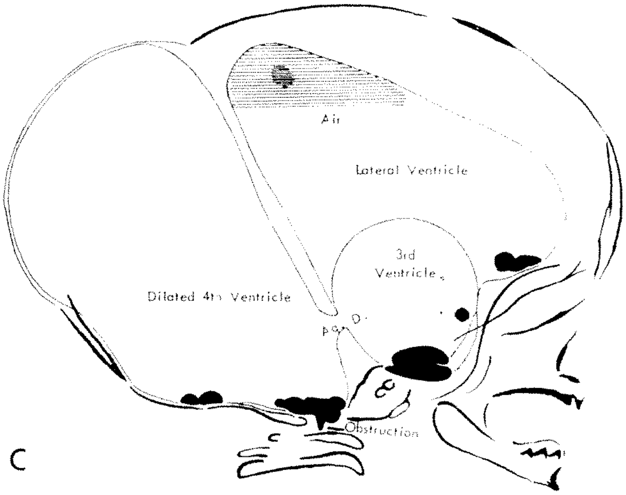


Fig. 5. Case 5. Air-pantopaque ventriculograms of a 3 week old baby. Hydrocephalus caused by block at craniocervical junction. (*A*) Brow-up, lateral ventriculogram. Dandy-Walker type of malformation clearly demonstrated. Arrows point to the lateral and fourth ventricle. (*B*) Upright lateral ventriculogram. Arrow points to obstruction at craniocervical junction. (*C*) Diagram of *B*.

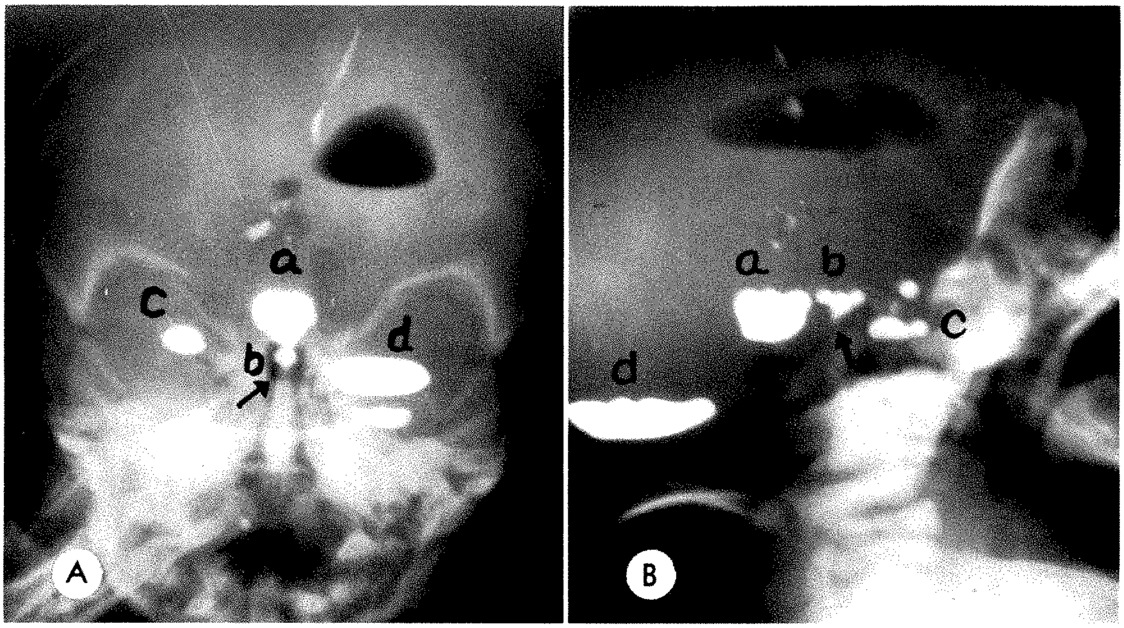


Fig. 6. Case 10. Air-pantopaque ventriculograms of a 2 week old baby with myelomeningocele showed evidence of hydrocephalus which was clinically unmanifested. (*A*) Upright anteroposterior ventriculogram. Block at aqueduct indicated by arrow. (*B*) Upright lateral ventriculogram. (a, b, c and d indicate pantopaque collections.)

space depends on the patency of the foramina of Magendie and Luschka. The structures at the craniocervical junction can be readily outlined and any anomaly or block at the level of the cisterna magna can be detected, whereas it may not be visualized on air studies.

In infants with normal pathways or communicating hydrocephalus, the pantopaque passes readily through the cisterna magna to the spinal subarachnoid space. The retention of a small amount of pantopaque in the ventricular system did not interfere with the function of a shunt that was applied shortly after the opaque studies in 6 patients of this series.

We feel that combined air-pantopaque ventriculography presents definite advantages over other methods of investigation. With the use of this technique, we were able to establish an accurate diagnosis in all of the patients by the direct demonstration of the site and type of malformation. This was of great help in establishing the surgical and prognostic criteria as well as the choice of the type of shunt procedure.

We included in our series, 6 infants with myelomeningocele and severe neurologic deficit related to their spinal pathology, but free of any clinical manifestations suggesting intracranial pathology. Pantopaque-air ventriculography was performed in an effort to detect any coexisting intracranial anomalies. In 4 of these infants it disclosed the presence of unmanifested hydrocephalus caused by atresia of the aqueduct, obliteration of the foramina of the fourth ventricle, or obstructive anomalies at the level of the craniocervical junction. The full investigation for intracranial pathology and the accurate demonstration of the defects present permitted significant evaluation of the status of the central nervous system and helped establish criteria for management

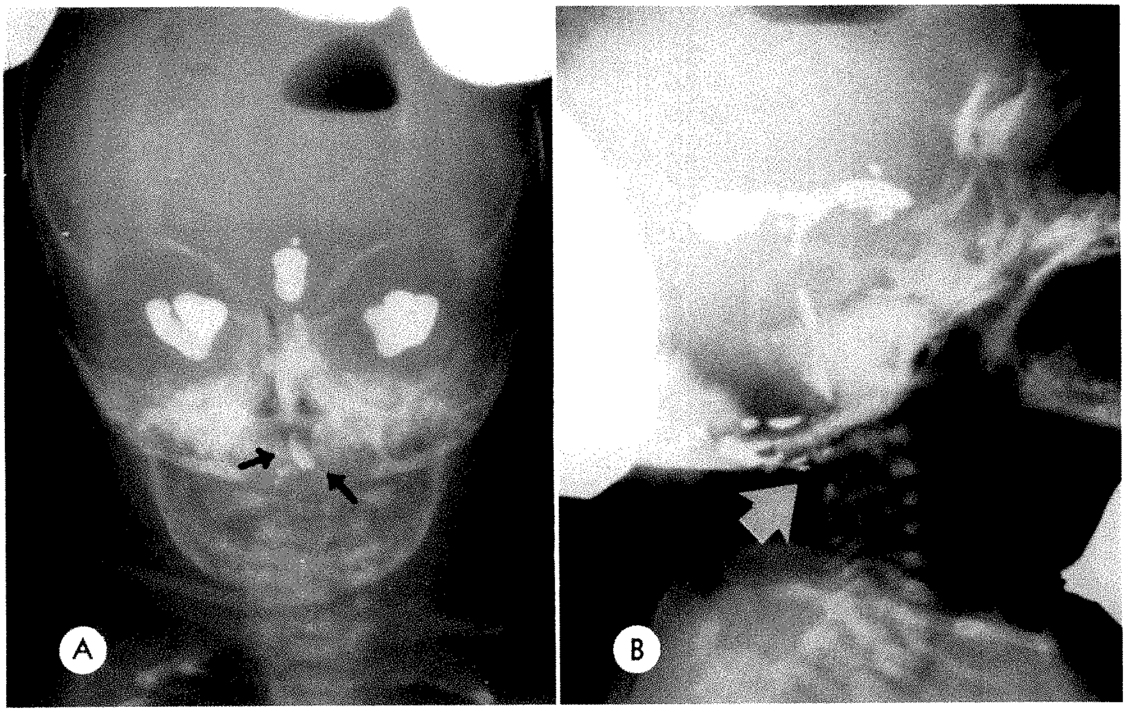


FIG. 7. Case 12. Air-pantopaque ventriculograms of a 3 week old patient with myelomeningocele. Note hydrocephalus. Pantopaque passed easily through aqueduct. Incomplete block found at craniocervical junction, indicated by arrows. (*A*) Upright anteroposterior ventriculogram. (*B*) Upright lateral ventriculogram.

and prognosis at a very early stage, before the development of clinical manifestations referable to the demonstrated posterior fossa malformations. Our studies showed that the anatomic causes of hydrocephalus in infants with myelomeningocele are the same as in infants with congenital hydrocephalus (compare Tables I and II), thus disproving the belief expressed by others that the Arnold-Chiari malformation is always responsible for its development.

SUMMARY

A study of the cerebrospinal fluid pathways by combined pantopaque-air ventriculography in infants with congenital hydrocephalus and myelomeningocele is presented. The advantages of this method of investigation are discussed. Combined pantopaque and air ventriculography provides not only a demonstration of the extent of the hydrocephalus but also the exact location and cause of the obstruction. In infants with myelomeningocele. it permits the disclosure of unmanifested hydrocephalus and coexistent intracranial malformations. The early detection of the latter is very important for the complete evaluation, management and prognosis of these cases.

The introduction of pantopaque into the ventricular system of infants did not produce an immediate reaction and did not precipitate deterioration of their clinical status. Retention of small amounts of pantopaque in the lateral ventricles did not interfere with the function of bypassing procedures.

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BILATERAL NEONATAL ADRENAL HEMORRHAGE*

By ORLANDO F. GABRIELE, M.D.,† *and* WILLIAM E. SHEEHAN, M.D.‡
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THE roentgen finding of adrenal calcification has been noted in a number of disease entities including tuberculosis, ganglioneuroma, neuroblastoma, pheochromocytoma, carcinoma, adenoma, generalized xanthomatosis, Niemann-Pick disease, *Echinococcus* cysts, and in pseudocysts. Adrenal calcification subsequent to adrenal hemorrhage is relatively frequent and probably accounts for many cases previously ascribed to tuberculosis.

The occurrence of adrenal hemorrhage is not uncommon[8,9,11] and has been reported with birth trauma, forceful resuscitation, infection, hemorrhagic disease of the newborn, severe burns, hemophilia, leukemia and even physiologic involution of the adrenal gland although the latter is of equivocal significance. Calcification subsequent to hemorrhage is well documented and has been reported to occur as early as 8 days following hemorrhage.[11]

Adrenal hemorrhage in the newborn is infrequently recognized clinically, only 1 of Snelling and Erb's[11] 15 cases being so diagnosed. In a later paper, Geppert *et al.*[2] also noted the sparsity of cases diagnosed antemortem.

The case presented afforded an unusual opportunity to observe the early clinical and roentgen manifestations of bilateral adrenal hemorrhage with a long-term follow-up showing massive bilateral calcification.

REPORT OF A CASE

J.B., a male patient, was born on March 26, 1954 and a review of the obstetrical history showed that the labor was full term and uneventful, with a vertex presentation. The baby was described as being somewhat listless and having a circumoral and peripheral cyanosis when out of oxygen. Examination of the skin revealed several petechiae and small areas of bluish discoloration.

At 48 hours, the baby still required oxygen and was noted to have a large cephalohematoma and bilateral masses in the kidney areas. Investigation of a developing jaundice revealed a direct bilirubin of 1.4 and indirect bilirubin of 32.5. Repeated Coombs' tests were negative. At this time, the hemoglobin was 13.5 gm. and the hematocrit 47 per cent. An intravenous pyelogram (Fig. 1) made at 14 days of age revealed normal renal function with both collecting systems displaced laterally and inferiorly by suprarenal masses. At this time, because the infant's clinical status had considerably improved, he was discharged and lost to follow-up until the present admission. In the interim, his growth and development were considered normal.

The patient was currently admitted on April 14, 1962, complaining of anorexia, nausea, vomiting and right upper quadrant pain of 7 hours' duration. Physical examination revealed a slightly dehydrated white, deaf-mute boy with pain on palpation of the right upper quadrant. The remainder of the functional inquiry and examination was unremarkable. His admission laboratory data were as follows: hemoglobin 13.8 gm; white blood cell count 13,000 with 87 per cent polymorphonuclear cells, 8 per cent lymphocytes, 2 per cent eosinophils and 3 per cent monocytes; alkaline phosphatase 15 units; bilirubin: total 1.0 mg. per cent, indirect 0.5 mg. per cent; SGOT normal limits; urinalysis normal; and serum electrolytes within normal limits. Anteroposterior roentgenography of the abdomen (Fig. 2*A*) and intravenous pyelography (Fig. 2*B*) revealed bilateral extensive adrenal calcification and what appeared to be at least one gallbladder calculus. Three attempts at cholecystography were made with resultant very poor opacification; two calculi were visualized. The patient's subsequent course in the hospital was unremarkable, the pain abating a few days after admission. Laboratory studies for possible hypoadrenalism included normal blood cortisol levels and urine 17 ketosteroid excretion. A glucose tolerance test was also normal.

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DISCUSSION

Adrenal hemorrhage is not rare, being found in about one per cent of autopsies on infants and children.[11] It may be unilateral or more commonly bilateral. Often it occurs in stillborn. Trauma of abnormal delivery is probably the most important factor in its causation. Although birth trauma, fetal size, and prematurity are frequently associated with hemorrhage, in Lundqvist's[6] review of 18 cases of adrenal hemorrhages, 5 followed normal deliveries.

Adrenal vascularity, size, and involution in the newborn may be large contributing factors in hemorrhage. Small bilateral adrenal hemorrhages are common in asphyxiated infants but the character of the hemorrhage is different. The time of onset of symptoms of acute hemorrhage in the adrenals is often the second to seventh day, corresponding to the age at which hemorrhagic disease of the newborn occurs. However, in Snelling and Erb's[11] 15 cases, there was definite association with hemorrhagic disease of the newborn in 1 case only.

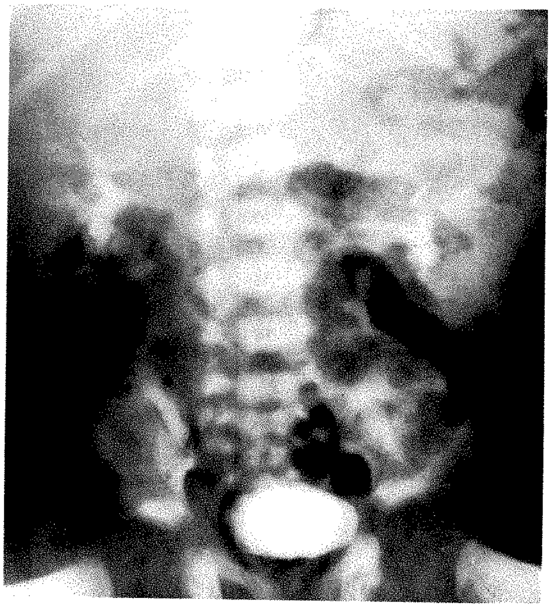

Fig. 1. Intravenous pyelogram made at 14 days of age reveals lateral and inferior displacement of the kidneys by suprarenal masses.

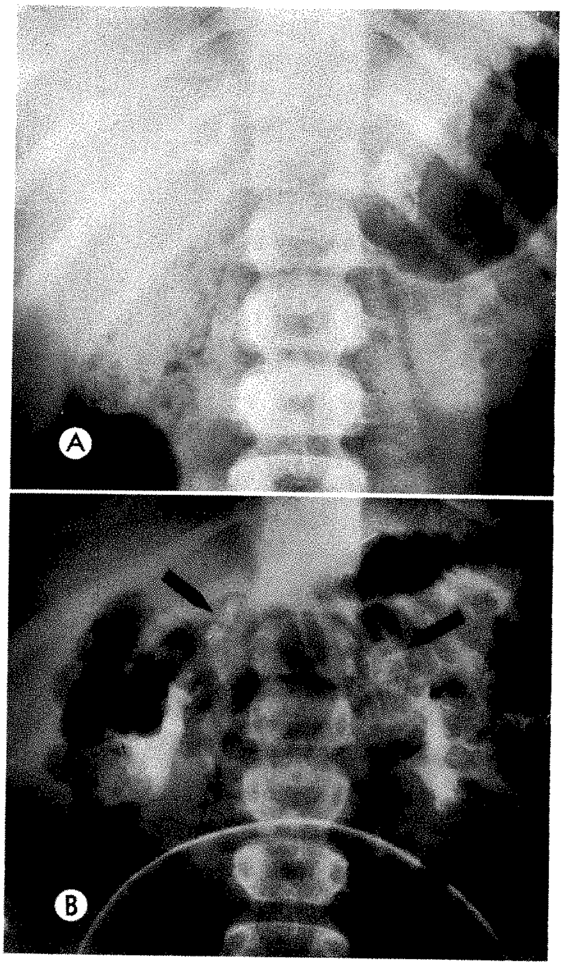

Fig. 2. (*A*) Plain roentgenogram of the abdomen obtained during the second admission at the age of 8 years shows massive bilateral adrenal calcification. (*B*) Intravenous pyelogram made during the second admission demonstrates the relationship of the adrenal calcification to the normal upper urinary tract.

Goldzieher *et al.*[3,4] were the first to clinically diagnose adrenal hemorrhage in the newborn. On the basis of 37 cases of adrenal hemorrhage in the newborn, 38 in older infants, and 6 additional cases, 5 of which were diagnosed during life, the clinical signs were divided into 2 categories: (1) manifestations of acute adrenal insufficiency: rapid respiration, pyrexia, purpura, metabolic upsets, convulsions, cyanosis, abdominal pain, vomiting, diarrhea, coma;

and (2) manifestations of acute hemorrhage: shock, collapse, weak pulse, cold extremities, pallor, air hunger, distended abdomen, and palpable masses. Symptoms, however, are variable from sudden death to no symptoms with all gradations in between.

Adrenal hematoma may simulate a tumor on both physical and roentgen examination.[7] This is particularly true when it presents as a unilateral mass without acute symptomatology. With adrenal cortical insufficiency and associated electrolyte imbalance, the clinical picture may simulate pyloric stenosis or high intestinal obstruction.[13]

Of the several interesting aspects presented by the reported case, we thought a few to be worthy of comment. In light of a statement by Hill and Williams[5] that no long-term survivals of massive bilateral adrenal hemorrhage are recorded in the literature, we found this case to be somewhat unique. Schaffer[9] reports a similar case with adrenal calcification following hemorrhage within 8 months. His case is illustrated by an intravenous pyelogram. Most previous cases described with adrenal calcification had abnormal birth histories and were thus presumed to have sustained adrenal hemorrhages at that time. However, usually no neonatal roentgen studies had been done. It is probable that a large number of patients with adrenal calcification, in the past frequently ascribed to tuberculosis, sustained adrenal hemorrhage shortly after birth. Similar to the 3 cases reported by Stevenson *et al.*[12] investigation of the above patient revealed a normal adrenal status in spite of what must have been extensive involvement of the gland during the perinatal period. The diagnosis of cholelithiasis made during the current admission is also of some interest as this disease is rather uncommon before puberty in the absence of hemolytic disease.

SUMMARY

A case of massive bilateral adrenal hemorrhage in a newborn infant is reported. The clinical course was benign with no sequelae other than the presence of massive bilateral adrenal calcification noted 8 years subsequent to the original episode.

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DELAYED SEQUELS TO RENAL INJURY IN CHILDHOOD*

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THE increasing importance of trauma as a cause of morbidity and mortality in childhood warrants consideration of acute and chronic effects of trauma on various organs and organ systems. This paper is concerned with injury to the kidneys. Renal injuries may occur as isolated events or as part of widespread injury to the body. In 1937, Campbell[1] reported 11 cases of renal injury in children under 15 years of age, occurring between 1914 and 1929; the incidence was 1:2,000 pediatric admissions. Between 1946 and 1962, 73 children were admitted to The Children's Hospital of Cincinnati because of renal injury. During the 16 year period, there were 118,000 admissions. The more recent incidence of renal injury thus has increased about 20 per cent to 1:1,600 admissions. Inasmuch as the frequency of all injuries has increased, it is not surprising that the frequency of renal injury has followed a similar pattern.

Our interest in the subject of sequels to renal injury in children was stimulated by a report from France[3] in which 3 cases and a possible fourth of definite renal atrophy following contusion were described. We had not regularly obtained late follow-up studies on our patients with renal injury because clinical sequels had not been observed, and the incidence of post-traumatic renal atrophy was not clear. We, therefore, undertook a follow-up examination of our cases of renal contusion in an effort to determine the frequency with which this type of atrophy could be identified.

INCIDENCE OF RENAL SEQUELS

Renal atrophy and distortion of the renal pelves following injury have been known for some time, but the great majority of the reports refers to studies in adults. Colston and Baker[2] found marked pathologic changes in the kidney or in the perirenal tissue in 13 patients studied at varying intervals after trauma to the region of the kidney. Only 1 of the 13 patients was in the pediatric age group, a boy of 13 years. Steinbock[10] found that 40 of 54 patients with renal injury, who were examined several years after the accident, had a normal renal pelvis and kidney. In 2 of the remaining cases, the affected kidney was without function, in another there was hydronephrosis and a fourth had pyelonephrosis and stone formation. Seven cases demonstrated minor changes in the renal pelvis which were thought to be a consequence of scar formation. Three cases were described as demonstrating "cavities." Of the 40 normal patients, 7 were children, all males under the age of 10 years. Three of the patients with renal pelvic deformities had been injured as children, but the follow-up studies were accomplished after maturity. According to Olsson,[6] the tendency to healing is great even with severe renal rupture. Nevertheless, he too noted renal atrophy following injury in which extravasation had taken place; the atrophy was observed within 5 months after the injury. Others[4,12] have reported changes 4 and 4½ months after injury.

Hypertension following rupture of the kidney can occur very quickly and has been reported to respond to nephrectomy.[5] Sobel[9] postulated that perinephritic hematoma is responsible for the hypertension by producing a constricting envelope around the kidney which compresses the organ. It was suggested that this compression was comparable to that which occurs in "cellophane perinephritis."[7] It is interesting that transient hypertension has been observed[11] after heminephrectomy and has been explained on the same basis. Strangely, it is difficult to find reference to late sequels of hypertension in individuals with atrophic kidneys following injury.

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Reports limited to renal injury in children are relatively uncommon. DuChamp and his associates[3] noted sequels of definite renal atrophy in 3 of 4 cases. The fourth patient had an abnormally small kidney, but because pyelographic studies were not taken at the time of the initial injury, the authors felt they could not differentiate between atrophy following trauma and a congenital hypoplastic kidney. Atrophy was characterized by a distinct change in renal contour and volume as noted in excretory urograms, with generalized or localized decrease in the area of the renal shadow on the affected side, and frequently a compensatory hypertrophy on the opposite side. The changes were noted in follow-up examinations as early as 6 months after the injury, and became more accentuated with the passage of time.

METHODS

The hospital records of children admitted with a diagnosis of possible renal contusion or injury were reviewed for the years 1946 through 1961. Those patients who had a clinical history or evidence of injury to the abdomen, who had hematuria or other evidence of renal injury, and who had intravenous pyelograms within the first 2 weeks following the injury were asked to return for repeat examination. Fourteen patients were available for study. There was no selection with regard to history of severity of the injury or the extent of damage to the kidney noted on the first excretory urogram. All except Case 10 had an excretory urogram made within 24 hours of the injury. Case 10 had a plain roentgenogram of the abdomen and a cystographic study following the injury; no extravasation from the bladder was noted and the patient was explored immediately on the basis of a clinical diagnosis of rupture of the right kidney. Excretory urography was performed 2 weeks after the injury.

All 14 patients had subsequent intravenous pyelographies, routine urinalyses and blood urea nitrogen determinations, and their blood pressures were recorded. Twelve of the patients were white males, one was a Negro male and one was a white female. The youngest patient at the time of trauma was 5 years and 1 month; the oldest was 14 years and 9 months of age. The median age was 12 years 1 month. The youngest at the time of the follow-up examination was 7 years and 10 months while the oldest was 20 years and 7 months; the median age at follow-up was 14 years 2½ months. All except Case 6 had been treated conservatively. The shortest follow-up was 10 months (Case 4); the longest was 13 years and 10 months (Case 6), and the median follow-up was 2 years 6 months.

RESULTS

The findings are summarized in Table 1. All patients had a normal blood pressure, urinalysis and blood urea nitrogen at the time of the follow-up examination. Nine of the 14 cases had abnormal excretory urograms at the time of the initial examination, but only 2 of these had definite abnormalities at the time of the follow-up examination. These 2 cases are described in detail below.

REPORT OF CASES

Case 6. J.F., a white male, aged 6 years 9 months, was admitted May 18, 1949 after being struck by an automobile. On physical examination a rigid and almost silent abdomen was found, in addition to contusions elsewhere in the body. Catheterized urine was grossly bloody. A plain roentgenogram of the abdomen demonstrated a poor renal outline on the right side, and because of a rapid drop in blood pressure and clinical findings consistent with intra-abdominal bleeding and trauma, the patient was explored for rupture of the right kidney. On

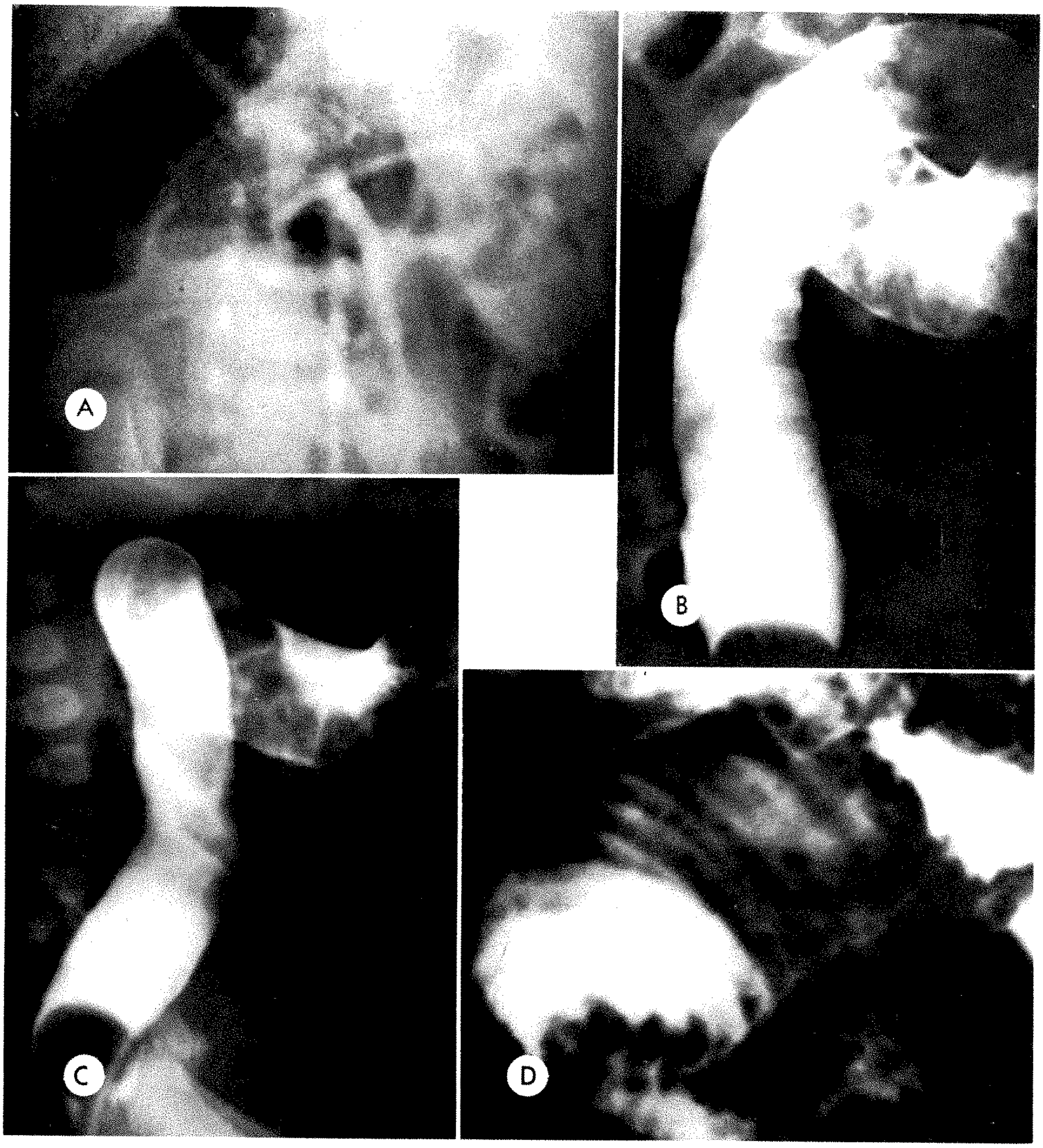

Fig. 1. Case i. (*A*) Moderate distention is present in several loops of intestine. (*B* and *C*) Barium enema studies show a normal caliber but grossly shortened colon. No transition segment is seen. (*D*) Spot roentgenogram of the ileum shows a markedly dilated loop of ileum. Fluoroscopically, repeated intussusception over a 20 minute period was observed.

undiagnosed. Enema studies had shown either a "normal" colon, as noted above, or a "microcolon." In our case, the chronic constipation had been clinically overshadowed by the picture of apparent high intestinal partial obstruction suggesting a malrotation.

Case ii. No. 161 44 69. This full term Negro male was transferred to the pediatric surgical unit at 2 days of age because of bile-stained emesis of 24 hours' duration. Meconium was passed at 36 hours. He continued to vomit intermittently though he had normal appearing bowel movements. Physical examination showed slight distention; rectal examination

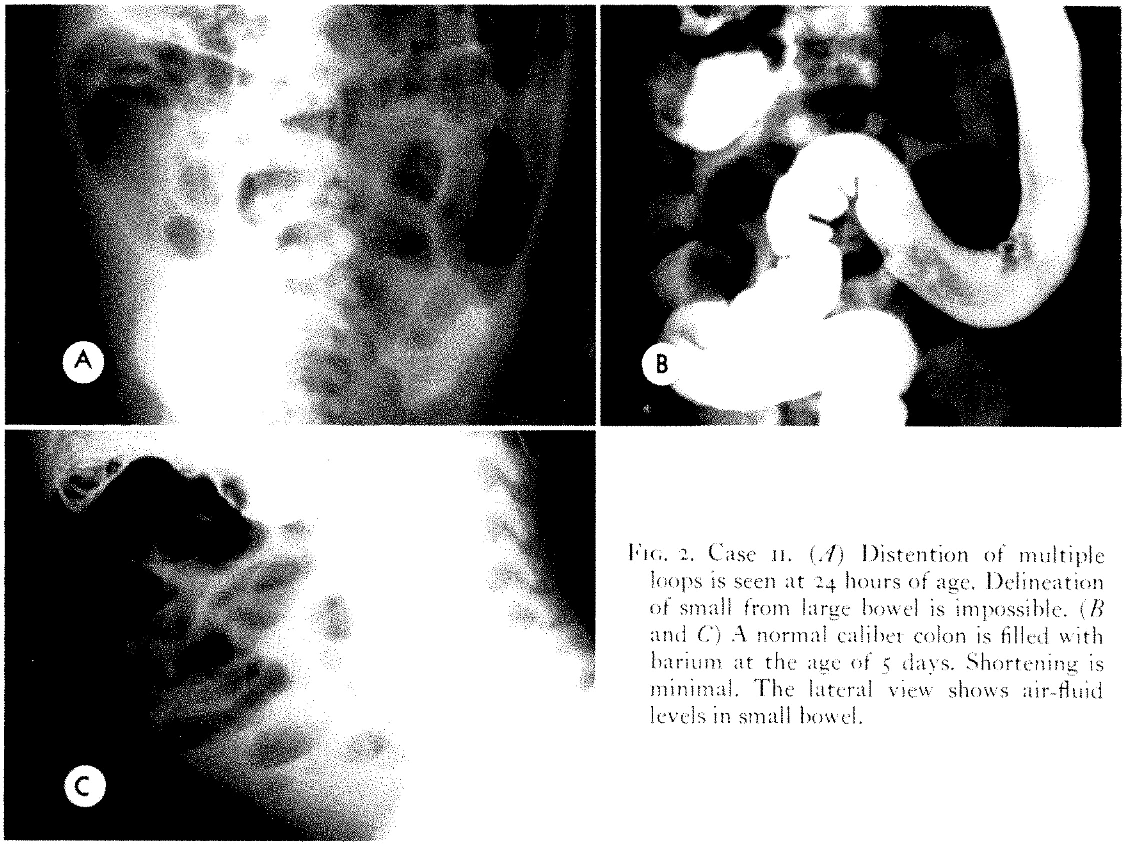

Fig. 2. Case II. (*A*) Distention of multiple loops is seen at 24 hours of age. Delineation of small from large bowel is impossible. (*B* and *C*) A normal caliber colon is filled with barium at the age of 5 days. Shortening is minimal. The lateral view shows air-fluid levels in small bowel.

showed soft stool. Laboratory studies were normal. A plain roentgenogram of the abdomen on the second day of life showed moderate dilatation and fluid levels in the intestine (Fig. 2*A*). He improved during the next 3 days but distention recurred on the fifth day and a barium enema examination was performed (Fig. 2, *B* and *C*). The colon was of normal caliber although slightly shortened; massive small bowel distention with air fluid levels was apparent on the enema studies. The diagnosis of aganglionosis of the colon and terminal ileum was suggested; low ileal stenosis was an alternate diagnosis. At operation, the small bowel was found to be dilated down to the terminal ileum; the latter appeared normal. The colon was not dilated though the sigmoid showed transition from a normal midsigmoid to a narrow distal sigmoid. Absence of ganglion cells in the terminal ileum was demonstrated by frozen section; ileostomy in the dilated ileum was performed but this too was found, on biopsy, to be aganglionic. The prolonged nature of the procedure and the infant's poor general condition led the surgeon to terminate the operation. It was hoped that the ileostomy was close to the transition from ganglionic to aganglionic ileum and would, therefore, function. The stoma turned dusky postoperatively and was clearly nonviable by the fifth postoperative day. Reexploration revealed gangrene of the terminal ileum and right colon. The gangrenous bowel was resected and an ileostomy was performed in the ganglionic ileum. Deterioration of the patient with sepsis and pneumonia caused his death at the age of 18 days.

Comment. This child was considerably younger than Case I. The colon was of normal caliber and only slightly shortened. The upper gastrointestinal tract was not studied. The marked dilatation of the small bowel and the normal appearance of the terminal ileum at operation suggest that the transition from dilated to normal ileum would appear on the roentgenogram as a zone of intussusception if peristalsis were present. Though the small bowel dilatation and the age of the patient could have suggested low ileal stenosis or an atypical late form of meconium ileus, both conditions show the "microcolon" of "nonuse" (Fig. 3), a colon of smaller caliber than the normal but of normal length and convolutions.

Case III. No. 163 38 70. A full term white female infant was transferred to Babies Hospital in May, 1963 at 4 weeks of age. Bile-stained emesis had been present from the first week of life. The bowel movements including the first passage of meconium are said to have been normal; however, submitted roentgenograms had shown dilated intestine. An upper gastrointestinal study done elsewhere on the tenth day of life was performed to exclude pyloric stenosis. The pylorus was normal. A roentgenogram taken 24 hours after the ingestion of barium showed marked stasis with retained esophageal, gastric and intestinal barium (Fig. 4*A*). By 15 days of life, marked distention was present with large air-fluid levels. On admission to Babies hospital, the child appeared chronically ill. Distention and pitting peripheral edema were noted. She was vomiting bile-tinged material. The serum albumin level was 3.8 gm./100 ml.; the other laboratory studies were normal. Repeat plain roentgenograms (Fig. 4*B*) showed multiple air-fluid levels with a small sigmoid colon. Prior to the barium enema study, the clinical and roentgenologic diagnosis was colonic aganglionosis with a probable sigmoid transition zone. Barium enema studies, however, showed a normal caliber but a grossly short colon with massive small bowel distention (Fig. 4, *C*, *D* and *E*). The changes were magnified by the erect position and were well seen in the Chassard-Lapine study. A diagnosis was then made of aganglionosis of the colon and terminal ileum.

Laparotomy revealed a short colon of normal caliber. The ileum was hypertrophied and dilated to within 8 inches of the ileocecal valve. Frozen sections showed aganglion cell transition from dilated to "normal" ileum. Ileostomy was performed. Though she did well for a week, diarrhea developed, the patient lost weight, and, as an emergency procedure, an ileoproctostomy was performed. She now has a deliberate attachment of ganglionic ileum to aganglionic rectum in the hopes that the latter, by preventing peristalsis, may slow transit time enough for intestinal absorption without causing enough obstruction to produce distention and possible enterocolitis, which so commonly follow partial obstruction in patients with aganglionosis.[2]

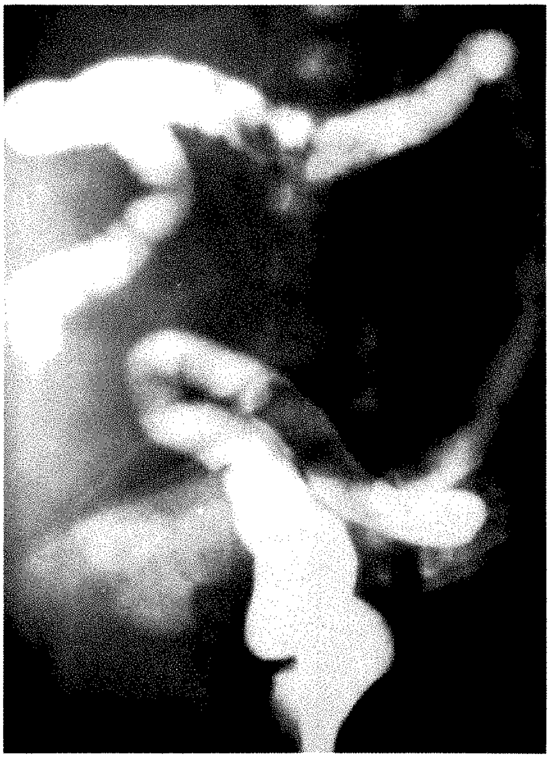

Fig. 3. The typical "microcolon" due to nonuse. This patient had meconium ileus secondary to cystic fibrosis of the pancreas. Though very small in caliber, the colon is not short.

Comment. The submitted roentgenograms suggested a colonic level of transition, probably in the sigmoid colon; the upper gastrointestinal study showed extreme stasis. These findings and the distention and bile-tinged emesis are characteristic of neonatal Hirschsprung's disease.[1,3,4,12] The enema examination clearly showed the normal caliber of the colon despite the gross small bowel distention. Ileal stenosis was excluded by the history and the roentgen findings. Unfortunately, a repeat upper intestinal barium study to demonstrate ileal intussusception was not done. The surgeon, given a definitive diagnosis, utilized rapid frozen section biopsies to confirm the diagnosis and to select the site for decompressing ileostomy. The decompensated state of the patient was apparent

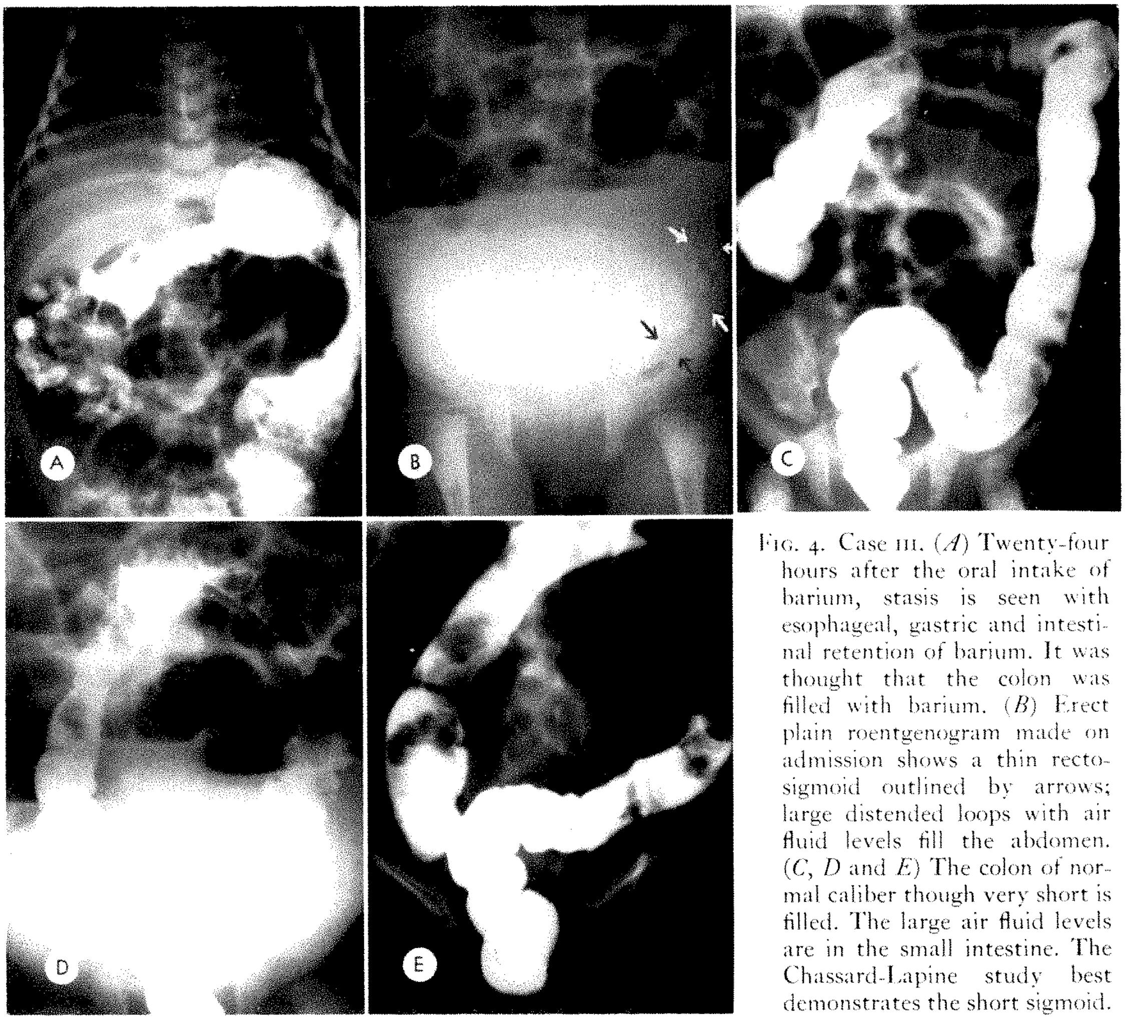

FIG. 4. Case III. (*A*) Twenty-four hours after the oral intake of barium, stasis is seen with esophageal, gastric and intestinal retention of barium. It was thought that the colon was filled with barium. (*B*) Erect plain roentgenogram made on admission shows a thin rectosigmoid outlined by arrows; large distended loops with air fluid levels fill the abdomen. (*C*, *D* and *E*) The colon of normal caliber though very short is filled. The large air fluid levels are in the small intestine. The Chassard-Lapine study best demonstrates the short sigmoid.

from the small bowel distention noted prior to the barium enema examination. If, however, an enema study had been done when the small bowel was not dilated, the short normal caliber colon might easily have been considered "normal."

A REVIEW OF 3 EARLIER CASES IN THE LIGHT OF THE ABOVE OBSERVATIONS

CASE IV. No. 62 71 45. A 5 week old Negro male was admitted in February, 1958 with abdominal distention, cachexia and dehydration. Alternating constipation and diarrhea had been noted since the first few days of life; a barium enema examination done elsewhere had suggested megacolon. On admission to Babies hospital, he was found to be chronically ill, and abdominal distention was noted. A serum albumin of 2.9 gm./100 ml. was found; all other laboratory studies were normal. A plain roentgenogram of the abdomen showed intestinal dilatation with a single markedly dilated loop in the right lower quadrant (Fig. 5*A*). A hypaque enema study revealed a short colon with a transverse and descending colon of normal caliber and a narrowed rectum and sigmoid (Fig. 5*B*). It was concluded that the dilated loop visualized on the plain roentgenogram was colonic. During a preoperative cleansing enema prior to colostomy, the patient went into shock. Perforation was suspected and repeat plain roentgenograms suggested intraperitoneal fluid. The patient died soon after. At postmortem examination, no perforation was found; massive pseudomembranous enterocolitis extended from the ileum and right colon to the narrowing noted on the enema study in the rectosigmoid region. A gross caliber change in the colon was

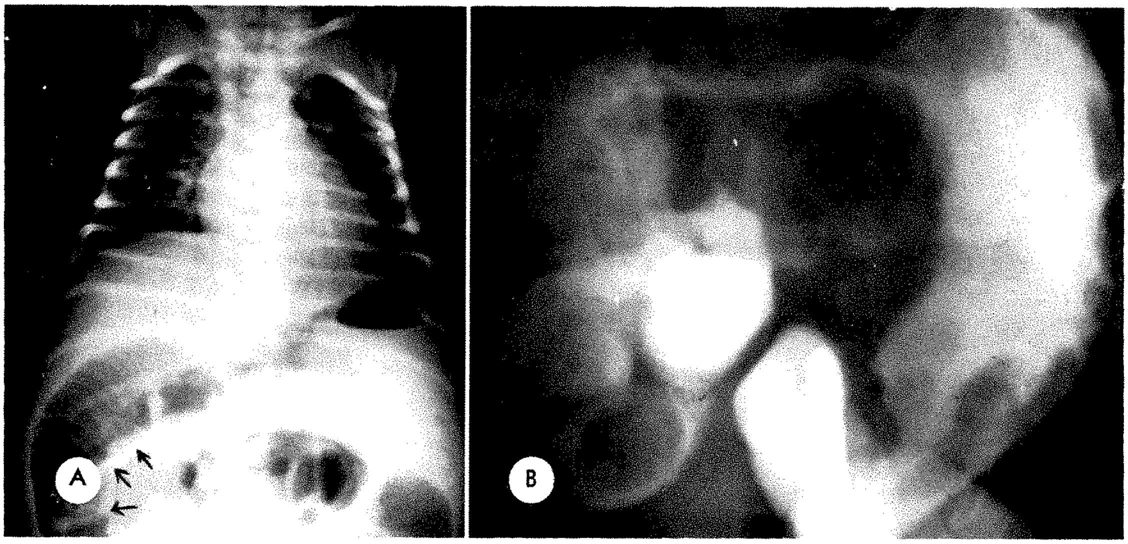

FIG. 5. Case IV. (*A*) A markedly stretched loop in the right lower quadrant shows valvular markings, indicating the small bowel. (*B*) Hypaque enema study shows a narrow rectosigmoid colon; the rest of the colon is short though of normal caliber.

also found in the rectosigmoid colon at necropsy. Microscopic study of the colon, however, revealed aganglionosis of the entire colon and terminal ileum. Death was attributed to colitis; the cleansing enema was thought to have contributed to the fluid and electrolyte problems already present from the extensive colitis.

Comment. When the plain roentgenograms that preceded the enema study were reviewed, the marked resemblance of the loop in the right lower quadrant to the ileal intussusception seen in Case I was noted. The short colon of normal caliber was present. The confusing aspect, still unresolved, was the finding on the enema study and at necropsy of rectosigmoid colon transition, both in caliber and in the distal limit of the colitis. The enterocolitis of Hirschsprung's disease[2] usually ends at the general area of transition from ganglionic proximal to aganglionic distal colon. The relative obstruction produced by the aganglionic segment is felt to be a causative factor in the colitis. Why this patient, presenting grossly with rectosigmoid levels, was found to have the entire colon and distal ileum involved with aganglionosis is unknown.

CASE V. No. 138 89 55. This patient, a full term white male infant, was explored elsewhere in August, 1958 at the age of 4 days for "low intestinal obstruction." No lesion was found. Bile emesis and constipation had been present prior to surgery. The obstructive signs persisted and the patient eviscerated 5 days after laparotomy. A repair and cecostomy were performed and the infant was transferred to Babies Hospital. He was pale and distended. Liquid fecal matter was draining from about the right lower quadrant stoma. An albumin level of 3.3 gm./100 ml. was the only unusual laboratory finding. A barium enema study showed a normal caliber colon filled to the midtransverse colon. A sigmoid colostomy was performed. No general exploration was possible because of dense adhesions; a biopsy of the sigmoid showed aganglionosis at the level of the stoma. The colostomy did not function. A retrograde hypaque study through the stoma showed no obstruction, and Dr. John Caffey suggested that the entire colon might be aganglionic. The opaque enema study (Fig. 6) showed a normal caliber somewhat shortened colon with a large filling defect in the right lower quadrant. Hypaque was noted to spiral about the defect. Temporary improvement in the patient's condition was followed by further distention. He was reexplored. The colon was neither hypertrophied nor dilated. An ileostomy was performed; however, the patient died soon thereafter following dehydration, shock and sepsis. Postmortem examination showed pseudomem-

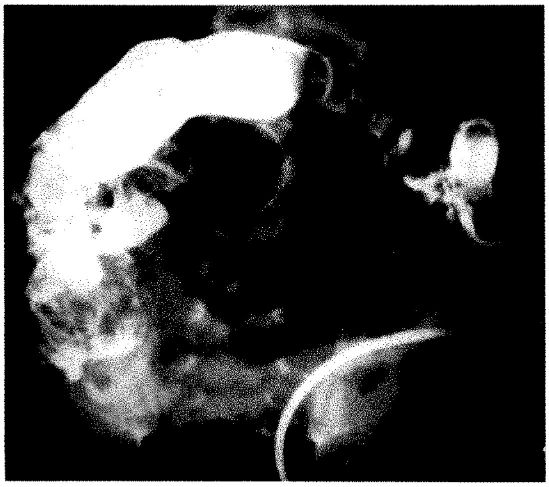

FIG. 6. Case v. Hypaque enema study through a sigmoid colostomy tube shows a colon of normal caliber though somewhat short; a spiralling of contrast material about a cecal filling defect is seen.

branous enteritis from midjejunum to distal ileum; the terminal ileum and colon, free of enteritis, were aganglionic.

Comment. As in Case II, the enema study demonstrated a normal caliber colon. Shortening was minimal. Small bowel distention was not prominent at any time. Clinical failure to recognize the problem led to delay, further debilitation and final lethal pseudomembranous enteritis. Frozen section biopsy would have revealed the extent of disease.

CASE VI (courtesy Dr. Virginia Kanick, St. Luke's Hospital, NYC). St. Luke's No. 300-237. A full term female infant was seen in April, 1953 at the age of 10 days because of distention, bile-tinged emesis and constipation. A barium enema study (Fig. 7) showed a short colon; the caliber was slightly smaller than normal though clearly not a microcolon. Distention increased but laparotomy revealed no signs of obstruction. No biopsy was obtained. A colostomy was performed but did not function. Four weeks later, after slow deterioration, the patient died. Postmortem examination showed aganglionosis of the entire colon and terminal ileum.

Comment. We reserve the term "microcolon" for the looping normal length tiny-caliber colon of "nonuse" seen in meconium ileus and ileal atresia. This patient's colon was small with gross shortening. In none of our cases of aganglionosis has there been a normal length microcolon. Again frozen section at the time of the colostomy would have clarified the problem and designated the stomal site.

DISCUSSION

A perusal of the surgical literature dealing with aganglionosis of the colon and terminal ileum, with the exception of a few instances[6,13,14] where frozen sections were taken during exploratory laparotomy because no obvious obstruction was found, reveals that the diagnosis has not been made prior to necropsy. Edelman *et al.*[7] were able to find only 30 reported cases up to 1960. The true number is probably higher, considering the great mortality rate

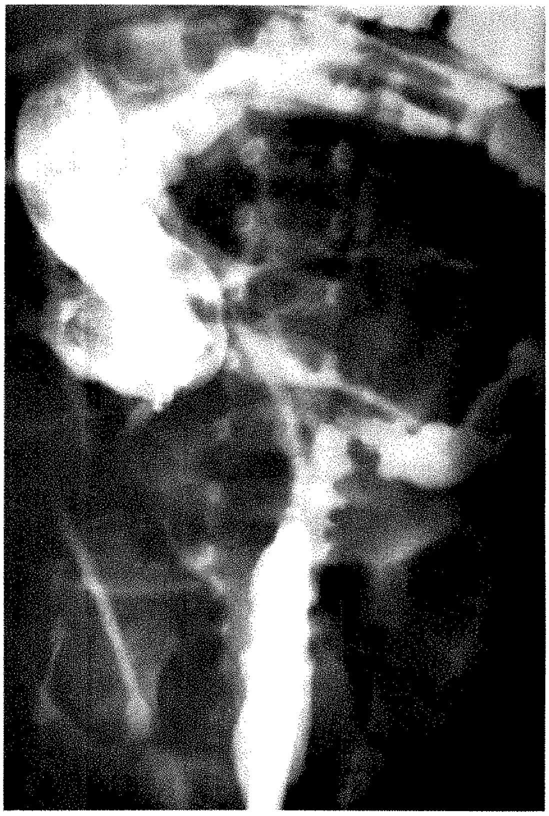

FIG. 7. Case VI. At 16 days of age, barium enema study reveals a short colon, most marked in the sigmoid region. The small intestine is greatly distended. The colon, though not as large in caliber as the average, is not a "microcolon."

in aganglionosis when it is unrecognized. The reasons for the problem of antemortem diagnosis are based on the clinical presentation. Were the patients to present with classic progressive constipation and distention, the "negative" laparotomy would have alerted most surgeons to obtain frozen or permanent section biopsies. This would confirm the diagnosis and establish the level of involvement. A review of our cases and the reported cases[6,7,12,13,14] shows that such a history is not typical. Many of the patients gain weight, distention is not usually marked and is intermittent rather than progressive. Bile-tinged emesis is common. The over-all impression is that of a rather mild partial small bowel obstruction. Some cases present as a high-type of obstruction resembling malrotation, as our Case I, others tend to mimic a mild ileal stenosis, as our Case II.

Many of the patients died before any surgery could be done. If operated upon when the small bowel was not dilated, a "normal" appearance of the colon and intestines might be found. In most reported cases no biopsy, frozen or regular, had been performed and the proper diagnosis was not made until after death.

Roentgenographic examination has been of little help in most of the reported cases.[1,6,7,12,13,14] Asked to look for megacolon, the radiologist searches for a colon transition zone and finds none. Unfortunately, the usual patient is not presented as a problem of suspected Hirschsprung's disease and only routine studies are done, consisting of an enema examination with immediate postevacuation roentgenograms or occasional upper gastrointestinal studies with, at most, a 2 hour roentgenogram.

The acutely ill patient presents a different problem. Conventional plain roentgenograms are of little help in differentiating dilated loops of small bowel from the colon. Air-fluid levels are frequently present. The usual practice is to do an enema examination with either barium or water soluble material. If an upper intestinal study were done, intussusception might be seen (as in Cases I and IV). Most often the enema study was described as "normal" in the reported cases[5,7,14] or in the smaller group of patients under 7 days of age as showing a "microcolon."[6,12,13] Dorman[6] and Swenson and Fisher[14] salvaged 5 patients in the latter group. Swenson and Fisher reported 2 patients with "normal" enema studies; frozen section established the diagnosis. Dorman[6] mentions 2 patients with "microcolon" and 1 with a "normal" enema study. These patients presented as atypical meconium ileus cases in the first week of life; no typical findings were seen at laparotomy and frozen section again established the diagnosis. Neither series suggests that the diagnosis of aganglionosis was considered preoperatively. The mortality rate in the review of Edelman *et al.*[7] through 1960 was 80 per cent. Dorman,[6] Swenson and Fisher,[14] and Sandegaard[13] account for most of the living cases.

We have not found any helpful roentgenographic criteria in the cases to date. Though "microcolon" is mentioned in the case reports of Dorman[6] and Bowden *et al.*,[5] among others, the reproduced roentgenograms do not show the small pencil-thick colon of nonuse (Fig. 3). In patients with long segment aganglionosis, a period as long as 3 months has elapsed before diagnosis and treatment or death resulted. Fairgrieve[8] reported a patient who at the age of 3½ years had the same zone of involvement. The "normal" appearance of these cases has been discussed to show the abnormal shape of the normal-caliber colon. Bowden *et al.*[5] show similar roentgen findings in 2 of 5 reported cases.

The shortening is real and confirmed by surgical examination. It is best seen in erect and Chassard-Lapine positions. The latter position, long used in adults to study the sigmoid, has become a valuable aid in cases of aganglionosis.

The exact premicroscopic identification of the transition from ganglionic to aganglionic segments is difficult if not impossible in these cases. One of our cases (Case IV) had an apparent surgical and roentgenographic and gross necropsy level in the sigmoid, though microscopic examination showed the ileal level. Experience with typical megacolon of the sigmoid or rectosigmoid level of transition has indicated the great value of delayed 24 and 48 hour roentgenograms[1] showing dilatation, air-fluid levels and retained contrast material down to the "transition" zone. As shown by Hiatt,[9] the functional obstruction of the aganglionic segment halts the peristaltic wave coming from the proximal ganglionic bowel. Hypertrophy and dilatation develop in the proximal segment. In the colonic form, the true transition is in the lower part of the dilated segment. This area dilates, even though aganglionic, because of the pressure imposed on it from above. Therefore, in these cases a colostomy cannot be performed in the lowest dilated bowel above the relatively narrow rectosigmoid. Frozen sections must be obtained to locate the ganglionic colon, or, as mentioned by Riker,[12] an immediate far proximal colostomy should be done. Riker suggests a transverse colostomy in such patients.

The demonstration of ileal intussusception on preoperative roentgenograms or the gross finding of ileal hypertrophy and dilatation above normal-appearing terminal ileum should alert the surgeon to search for ganglion cells in frozen sections. Many cases are reported where at operation compensation with absence of dilatation was noted.[6] The gross normal findings point out the waxing and waning characteristics of the disease. The roentgenographic findings parallel the state of the disease in its natural course.

Peristaltic stimulants such as prostigmine may be helpful. It may be possible to provoke dilatation in the ganglionic loops by causing peristaltic waves to beat against the irregularly spastic segment of aganglionic intestine. Hiatt[9] showed that unoperated on patients with rectosigmoid megacolon responded with hyperperistalsis proximally and irregular spasms in the rectosigmoid. It seems reasonable that a similar provocation in the long segment cases might induce the intussusception pattern in the small bowel. What remains puzzling is the intermittent nature of the decompensation. Why do patients go 4 to 10 weeks (or even $3\frac{1}{2}$ years) before serious trouble develops? This is even more striking when compared to the fact that patients seen at 2 to 3 days of life with rectosigmoid megacolon have huge dilated colons, enterocolitis and lethal outcomes. The low colonic group of patients may live with their disease into adult life. No long segment cases have been seen beyond early childhood.[7]

Although aganglionosis generally affects 4 times as many males as females, the long segment variety shows a slight predilection for females. Slightly over $\frac{1}{2}$ of Edelman and co-workers'[7] collected cases were girls. Our series contains 4 males and 2 females. In general, congenital defects have not been noted as in Hirschsprung's disease. These are otherwise normal infants.

The cause of aganglionosis remains unknown. It has been possible, in animals, to render a small segment of sigmoid ischemic, either by isolating a loop and perfusing it with an electrolyte solution during a period of several hours,[10] or by rapidly injecting a bolus of neurotoxic contrast material.[11] The small ischemic segment will then develop localized aganglionosis in the absence of infarction, scarring or other inflammatory changes. No such vascular compromise has been found in the human. In all of our cases, as in those of Bodian *et al.*,[3,4] Berman,[1] Riker[12] and Swenson and Fisher,[14] no "skip" areas were found, the aganglionosis extending from the most proximal aganglionic level all the way to the anorectum.

Current treatment is by a ganglionic ileostomy; later an ileoproctostomy is performed.[14] The problem of an ileostomy with the accompanying diarrhea and loss of electrolytes and protein is immense. Our Case I is barely surviving. Case III was doing so poorly with an ileostomy that a deliberate attachment of ganglionic ileum to an aganglionic rectosigmoid was performed in the hope of slowing intestinal transit time. It remains to be seen if enterocolitis will develop behind the relative obstruction of the rectosigmoid.[2]

SUMMARY

1. Colonic and terminal ileal aganglionosis presents in the first 3 months of life as intermittent small bowel obstruction. Clinical suspicion is led to possible malrotation, bands or webs. Constipation and progressive distention are the exception.

2. The barium enema study shows a colon of normal caliber but not of normal length. The flexures and loops most obviously reflect the shortening.

3. Ileal intussusception may be seen on plain roentgenograms and upper gastrointestinal barium studies.

4. "Negative" laparotomies will decrease as increased use is made of frozen section biopsy techniques to confirm the presence of ganglion cells.

5. Only prompt ileostomy will save such patients.

6. The long segment variety of aganglionosis, though not common, is more unrecognized than extremely rare.

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VOLVULUS OF THE SIGMOID IN CHILDREN*

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VOLVULUS of the sigmoid is a well known clinical entity in adults but it is less common in children. We have seen 6 cases of sigmoid volvulus in children; all had similar clinical and roentgen findings. The comparative rarity of juvenile sigmoid volvulus is indicated by the fact that 190 cases of ileocolic intussusception were seen during the same period.

REVIEW OF THE LITERATURE

In the adult, sigmoid volvulus usually occurs during late middle age and represents a minor percentage of all intestinal obstruction cases.[1–4, 9, 11] Redundancy of the sigmoid, chronic constipation, and excessive roughage in the diet have all been mentioned as predisposing causes.[1,2,12,13] The male predominance appears to be well established although the ratios vary.[2,6] The classic appearance on plain roentgenograms is a dilated sigmoid loop which fills most of the abdomen and on barium enema study a "snake head" deformity at the rectosigmoid level.[1,2,4,8,12,13]

Few children have been reported with a sigmoid volvulus. Dean and Murry[6] described this lesion in a 4 year old who also had megacolon. There are 2 other reports of patients with a dilated and obstructed sigmoid loop.[5,10] We found no report of hydrostatic reduction of a sigmoid volvulus.

REPORT OF CASES

CASE I. K. M., a $3\frac{1}{2}$ year old boy, had intermittent abdominal pain for 2 weeks prior to admission. On the day of admission, after straining at stool, he had cramping pain which lasted about a minute and recurred about every 10 minutes. His stools were normal.

Abnormal physical signs were limited to the abdomen which was slightly distended and in which a 2 by 3 inch mass was felt in the left lower quadrant. There was tenderness on

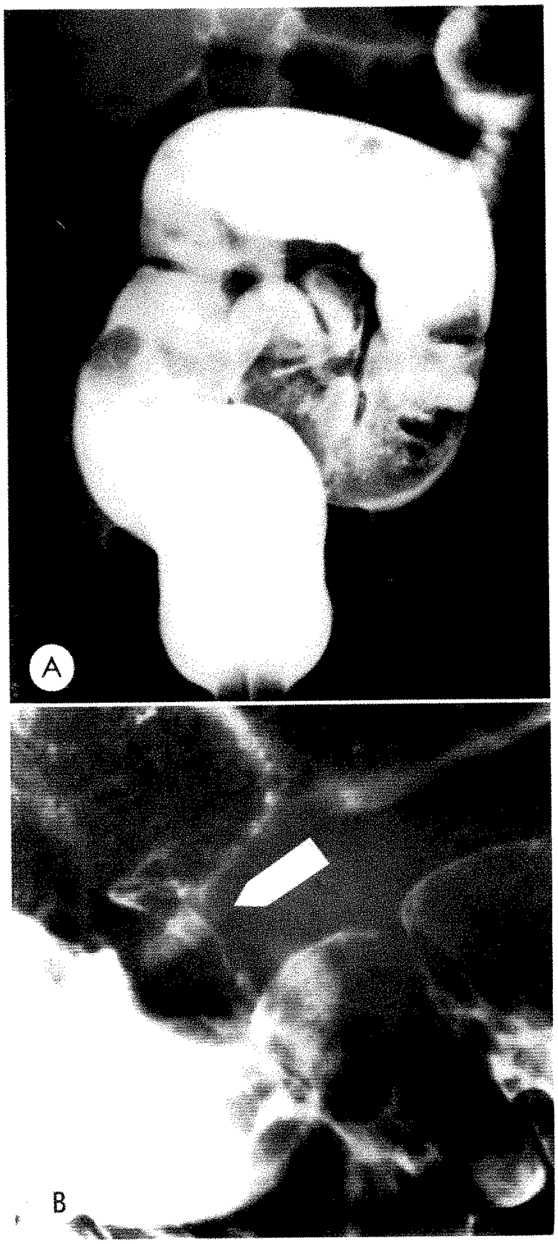

FIG. 1. Case II. Barium enema study shows a redundant sigmoid loop and a partially obstructed proximal end. (*B*) Spot roentgenogram shows the "twisted point" configuration at the site of the volvulus.

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palpation and spasm of the abdominal muscles.

The laboratory findings were not remarkable. On barium enema study the proximal sigmoid was obstructed for several minutes. The rest of the colon was normal. Following the barium enema examination, the pain disappeared and after 24 hours of observation the patient was sent home.

Case II. J. A., a 6 year old boy, suddenly experienced pain in the left lower quadrant of the abdomen while swimming, 4 hours before admission. When he walked the pain increased. He did not become nauseated. He had not had a bowel movement for 2 days.

Physical findings were negative except for a palpable liver and rigidity and tenderness in the left lower quadrant of the abdomen.

Laboratory findings were normal. A barium enema study demonstrated complete obstruction at the mid-portion of the descending colon (Fig. 1, *A* and *B*). However, the barium suddenly filled the rest of the colon after hydrostatic pressure was applied for a few minutes. A diagnosis of sigmoid volvulus, probably reduced, was made. At laparotomy a redundant sigmoid and descending colon were found. The sigmoid was thick and edematous in contrast to the rest of the colon which was normal.

Case III. S. M., a 4 year old boy, suffered from cramping abdominal pain of 4 hours' duration which had been preceded by "fussiness" and loss of appetite.

On physical examination, the only positive finding was a flat rigid abdomen. Tenderness was present but was not localized. No masses were palpated and the bowel sounds were active.

Laboratory findings were normal excepting a leukocytosis of 13,000 with 73 per cent polymorphonuclears, 26 per cent lymphocytes and 1 per cent monocytes. The barium enema study showed an obstructed distal sigmoid which suggested sigmoid volvulus (Fig. 2). During continued observation, the barium filled a dilated loop of sigmoid and subsequently extended into the transverse colon. The patient was relieved of symptoms and after 24 hours of observation he was dismissed.

Case IV. R. N., a 3½ year old boy, developed cramping abdominal pain after a loss of appetite. There was no vomiting.

Physical examination showed a temperature of 101.8° F. and cervical lymph node enlargement. A small amount of blood was found on rectal examination. Laboratory findings were normal. A barium enema study demonstrated a long sigmoid loop which was obstructed at its upper end. A diagnosis of sigmoid volvulus was made. After a few minutes of hydrostatic pressure, the volvulus was reduced and the symptoms disappeared. Two days later the patient's tonsils became red and swollen. He responded to medical therapy and was discharged in a few days.

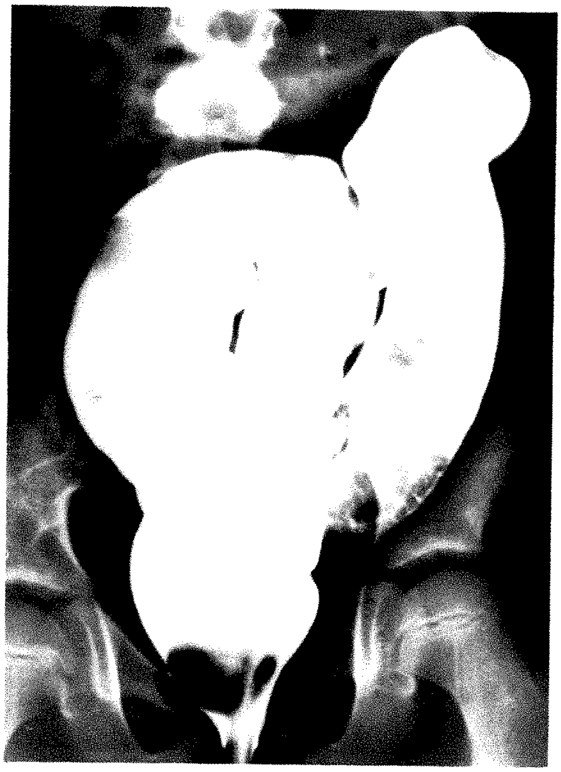

Fig. 2. Case III. Roentgenogram shows the redundant sigmoid with obstruction at the proximal end. "Twisted point" configuration is plainly visible.

Case V. R. S., a 7 year old boy, complained of intermittent pain in the left side of the abdomen which developed 2 days before hospitalization. The bowel movements were normal each day. Three hours before admission he suddenly doubled up with left lower quadrant pain so severe that he cried out. There was no vomiting.

Physical findings were normal excepting moderate distention of the abdomen with

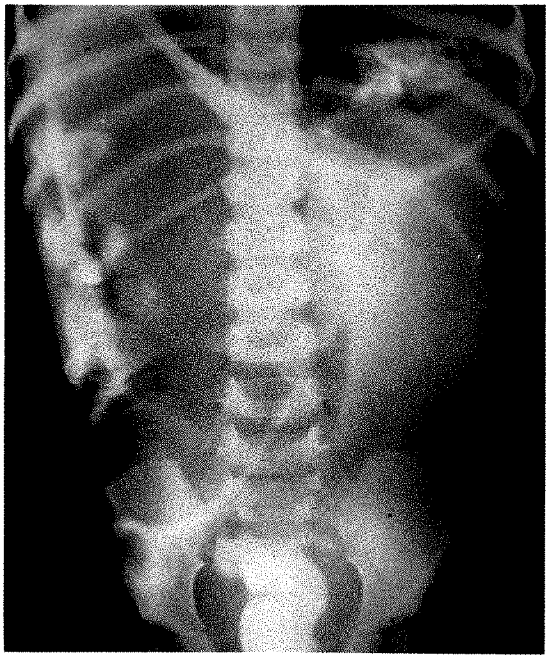

FIG. 3. Roentgenogram of an infant showing the adult type pattern of dilated sigmoid and "snake head" deformity at the obstructed rectosigmoid junction. It is the only example we have seen of the adult picture of sigmoid volvulus in an infant. It is an old roentgenogram from our files for which we have no history.

voluntary muscle spasm on the left side. Rebound tenderness was not elicited and no masses were felt. Normal bowel sounds were heard. Rectal examination revealed marked tenderness with a possible mass at finger tip level.

Laboratory findings were normal. Barium enema study showed that the sigmoid was narrowed and partially obstructed, in a pattern characteristic of sigmoid volvulus.

The abdomen was explored soon afterward. There were peritoneal bands across the sigmoid. There was no volvulus, but the sigmoid was edematous and the surgeon thought that its blood supply had been compromised recently.

CASE VI. J. M., an 11 year old boy, began to have pain in the left flank and left lower quadrant 2 hours before admission to the hospital. He vomited twice. On the day of admission, he had had no bowel movements but before this, his stools had been normal. He had undergone no previous surgery but had recovered from hepatitis a year before admission.

He appeared acutely ill. Positive findings were limited to the abdomen which was flat, slightly tense, and generally tender. Marked tenderness was noted over the left flank and left lower quadrant. A questionable ovoid mass was felt in the left lower quadrant. Bowel sounds were normal. A rectal examination was unsatisfactory because of fecal matter in the rectum.

Laboratory findings were normal excepting slight leukocytosis of 10,800 with a differential of 84 per cent polymorphonuclears, 11 per cent lymphocytes and 5 per cent monocytes. Urinalysis was normal excepting 6 to 8 white blood cells per high power field on microscopic examination.

Plain roentgenograms of the abdomen showed fecal material in the rectum and sigmoid colon. No mass was visible. One short loop of bowel—apparently sigmoid—contained gas. A barium enema study, under fluoroscopic control, showed obstruction to the flow of barium in the proximal sigmoid where a typical "snake head" deformity was seen. Complete reduction of the volvulus was not accomplished. The patient evacuated the enema, felt relief of the pain, and was re-examined fluoroscopically. This time there was no obstruction to the flow of barium and the entire colon was outlined and felt to be normal except for mild redundancy of the sigmoid.

The patient's course was uneventful. He was kept for observation 24 hours, fed a clear liquid diet, and discharged asymptomatic the following day.

ROENTGEN FINDINGS

The roentgen findings are similar in all cases. A nondiagnostic gas pattern which may include several loops of small bowel is demonstrated on the scout roentgenogram. The large single sigmoid loop, so characteristic of the adult patients is usually not seen (Fig. 3). Barium enema studies show a constant flow of the barium through the rectosigmoid junction. The sigmoid loop fills without difficulty and usually contains no feces. It may be redundant but this is not necessarily significant since a long sigmoid is common in normal children. The head of the barium column stops abruptly at the upper end of the sigmoid loop where it tapers to a twisted point (similar to the "snake head" configuration seen in adults at the lower end of the loop). The head of the column will often remain at this level for several minutes; this is more prolonged than the normal temporary delay which often occurs at this level. In one instance the actual untwisting of the volvulus was visible fluoroscopically. In the others after the delay there was a sudden rush of barium into the more proximal part of the colon. In each case the patients' symptoms disappeared immediately after the head of the column passed above the sigmoid.

SUMMARY

Six cases of volvulus of the sigmoid in children are reported. All were males between the ages of 3 and 11 years. All had acute abdominal pain. They were thought to have intussusception clinically. In each case the volvulus was reduced easily by retrograde hydrostatic pressure and the patient had no further symptoms. Two of the 6 patients were explored after hydrostatic reduction and the sigmoid loops appeared edematous. The roentgenographic findings of sigmoid volvulus in these children differed from those reported in adults. The cardinal finding was a twisted narrowing of the proximal sigmoid which straightened out after hydrostatic pressure was applied. This was followed by filling of the more proximal bowel. The gas-filled sigmoid loop and the "snake head" deformity caused by the obstruction at the distal end of the sigmoid loop, which are characteristic in the adult, were not demonstrated in these patients.

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THE OSMOTIC EFFECT OF WATER SOLUBLE CONTRAST MEDIA ON CIRCULATING PLASMA VOLUME*

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DIATRIZOATE methylglucamine (gastrografin) possesses many qualities of an ideal medium for visualization of the gastrointestinal tract.[1,3] However, recent clinical experience indicates that infants undergoing investigation with this material may succumb to a severe state of hypovolemia.[2] This observation stimulated our investigation of the physicochemical properties of this substance.

MATERIALS AND METHODS

In a preliminary study, 9 mongrel dogs weighing 10 to 12 kg. were anesthetized with intravenous nembutal and baseline plasma volumes were determined by use of the Volumetron* and radioactive iodinated serum albumin. The 9 dogs were subdivided into 3 groups for investigation; a control group which was anesthetized and did not receive gastrografin, a second group of dogs which was kept in a fasting state prior to investigation, and a third group which was fed subsequent to instillation of the medium. A nasogastric tube was placed into the stomach of each dog and in groups 2 and 3 undiluted gastrografin, 6 cc. per kg., was instilled into the tube. Serial hematocrits and plasma volumes were measured. Fluoroscopic examination commenced with the introduction of the gastrografin into the gastrointestinal tract. Coincident with its passage into the small bowel, there was a decrease in the density of the medium (Fig. 1 and 2). This decrease in opacity could be correlated with a progressive fall in the circulating plasma volume (Fig. 3). In the control group, no change in plasma volume was noted during the 6 hours of observation. There was no apparent difference between the 2 other groups studied. The decrease in plasma volume was sustained over 3 to 4 hours. When expressed as a percentage loss of the total circulating volume, the figures ranged from 15 per cent to 30 per cent.

The findings of a depletion in plasma volume associated with the presence of gastrografin in the intestinal lumen stimu-

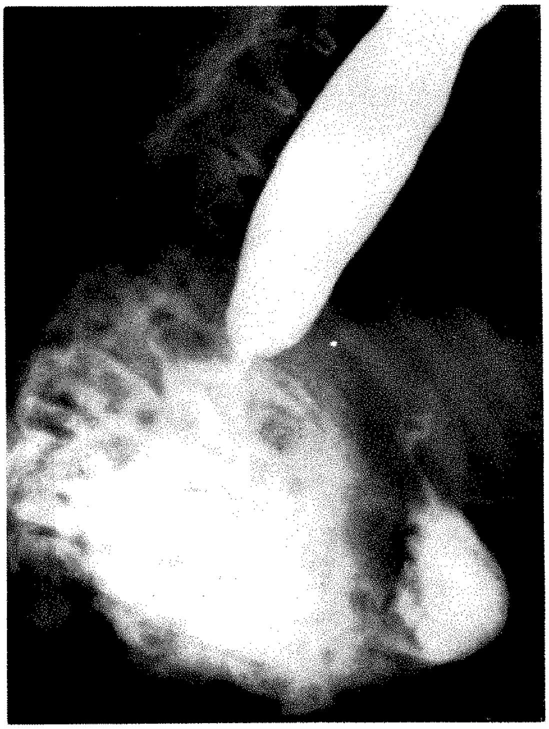

FIG. 1. Gastrografin beginning to fill duodenum.

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lated a second investigation to determine what, if any, relationship existed between the osmotic activity of gastrografin and the exchange of fluid between the vascular compartment and the intestinal lumen. Osmolar activities were measured by the method of freezing point depression, using a Fiske Osmometer. In this investigation, 3 groups of dogs were used and in each group 4 animals were studied. In Group I, the animals ranged from 4 to 7 kg.; in Group II, from 10 to 15 kg.; and in Group III, from 22 to 25 kg. In each group, closed isolated ileal loops with intact vascular pedicles were established. Using this type of preparation, it was possible to instill any medium into the lumen of the closed loop by means of a purse-string suture and needle, and the studies could then be commenced on the loop fluid in a dynamic state, when a continuous exchange was taking place within the capillary walls and vascular bed of the intact pedicle.

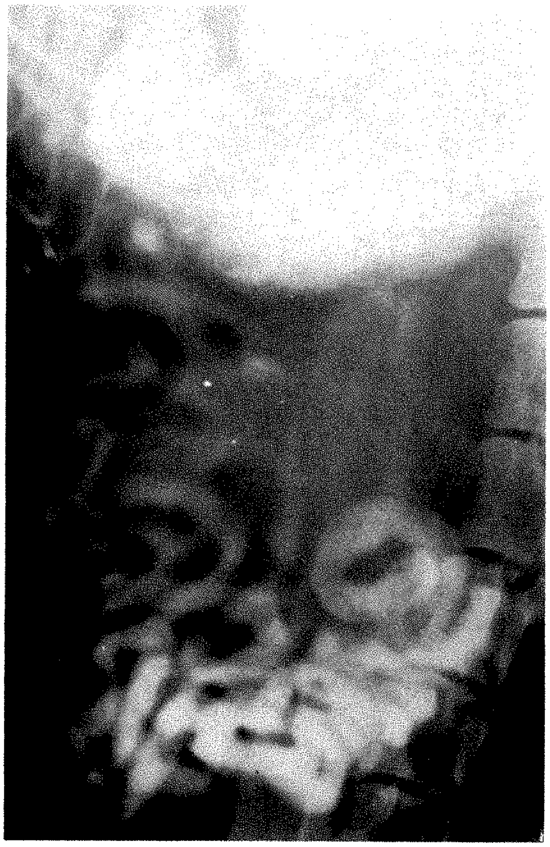

Fig. 2. The opacity is decreased as the medium passes through the small intestine.

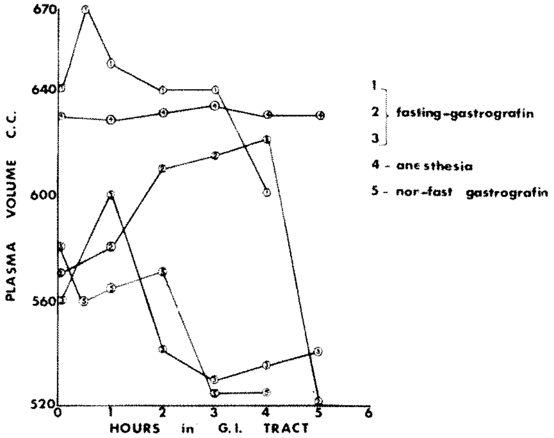

Fig. 3. Gastrografin study. A sustained fall in circulating plasma volume was noted in all groups studied.

Eighteen cubic centimeters of gastrografin was instilled into each loop and the serum plasma volumes and the osmolarities of the loop fluid were measured over the next 2 hours. Grossly, one could see that the loop during this elapsed time became turgid and swollen with diminution in the peristalsis (Fig. 4 and 5). After 2 hours, the loop became so tense that the pulsations in the small vessels were completely obliterated and the circulation was partially compromised (Fig. 6).

RESULTS

Gastrografin has an osmolarity of 1,900 milliosmols per liter (approximately 6 times that of normal serum). Samples of fluid were withdrawn from the loop at 15 minute intervals over a 2 hour period. There was a progressive decrease in the osmolarity of this fluid, as the volume of the fluid in the loop increased (Fig. 7). The estimated and calculated loop osmolarities for any given dog could be compared and were found to be within 3 per cent (Table I). These measurements formed the groundwork for determining the effect of osmotic changes on circulating plasma volume. The dogs in Group I weighed 5 to 7 kg., in Group II 10 to 15 kg., and in Group III 20 to 25 kg. Gas-

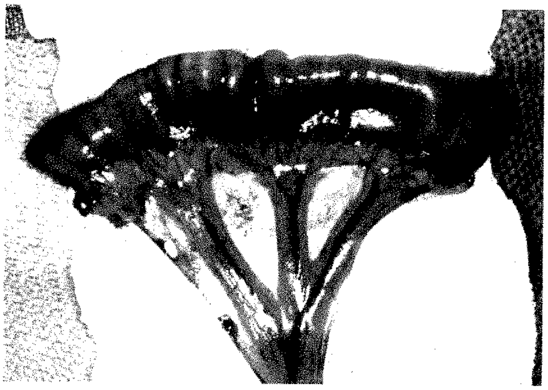

Fig. 4. The isolated ileal loop immediately after instillation of 18 cc. of gastrografin.

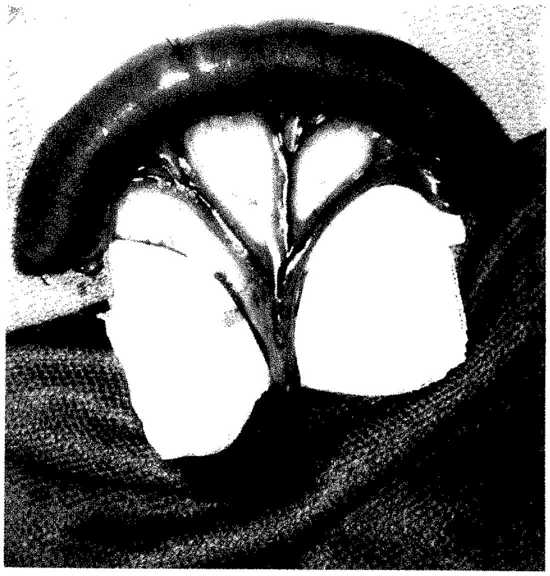

Fig. 6. The loop is tense with decreased capillary pulsations 2 hours after instillation of gastrografin.

trografin was instilled into each loop and specimens were withdrawn from the loop. The volume of fluid which accumulated in the loop was measured and compared with the amount of fluid lost from the circulating plasma volume or the plasma deficit.

In the large and medium sized animals, there was a progressive increase in the loop fluid which paralleled the decrease in circulating plasma volume. These dogs showed no clinical signs of shock.

In the small animals, where the average weight was only 6 kg., there was twice as much plasma lost from the circulating volume as could be accounted for in the volume of fluid transferred into the loop. These animals were in shock with rapid pulses and depressed blood pressures (Fig. 8). The discrepancy between the loop volume and plasma deficit in the small animals represented plasma lost or pooled in other areas of the gastrointestinal tract. This is a well established finding in hypovolemic or endotoxic shock.

The volume of fluid transferred into the loop after 2 hours of perfusion was found to be essentially the same for all of the animals studied, regardless of the size.

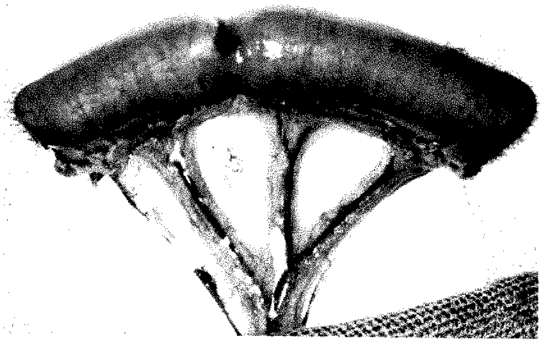

Fig. 5. Fifteen minutes after the gastrografin instillation.

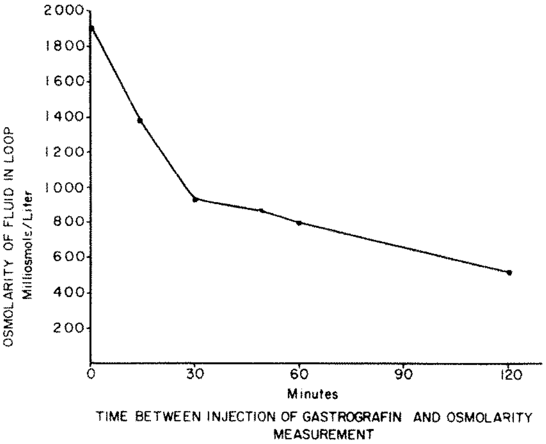

Fig. 7. The osmotic effect of gastrografin on the circulating plasma volume. After 2 hours of loop perfusion, the osmolarity of the fluid has decreased to 600 milliosmols.

Table I

13 kg. dog with a closed ileal loop	
Gastrografin instilled	24 cc.
Loop fluid withdrawn after 30 minutes	52 cc.
Net volume of fluid transferred into loop	28 cc.
Dilution ratio	$\frac{24}{52}$
Estimated loop osmolarity	$1{,}900 \times \frac{24}{52} = 900$ mosm./l.
Calculated loop osmolarity	930 mosm./l.

DISCUSSION

Gastrografin, because of its relatively high osmolarity, presents itself to the capillary membrane of the bowel wall as an osmotic force. The capillary wall acts as a semipermeable membrane allowing passage of fluid across into the bowel lumen to balance or neutralize the osmotic gradient exerted by gastrografin (Fig. 5).

Since the amount of fluid transferred across any semipermeable membrane is dependent upon (1) the surface area of the membrane, (2) the osmotic gradient, and (3) the time of surface contact, the reduction in circulating plasma or that portion lost into the bowel would depend upon (1) the level of obstruction, (2) the type and degree of obstruction (mechanical or paralytic), and (3) the amount of gastrografin ingested.

Thus, the apparent clinical effects of the instillation of gastrografin into the gastrointestinal tract are also related to the weight of the subject, and, therefore, the initial circulating plasma volume. The plasma volume may be severely altered by malnutrition and chronic disease states, thus indicating that weight alone is not the sole factor to be considered before using gastrografin.

SUMMARY

1. Gastrografin possesses a high osmolar activity which is capable of exerting a definitive force upon the circulating plasma volume (Fig. 9).

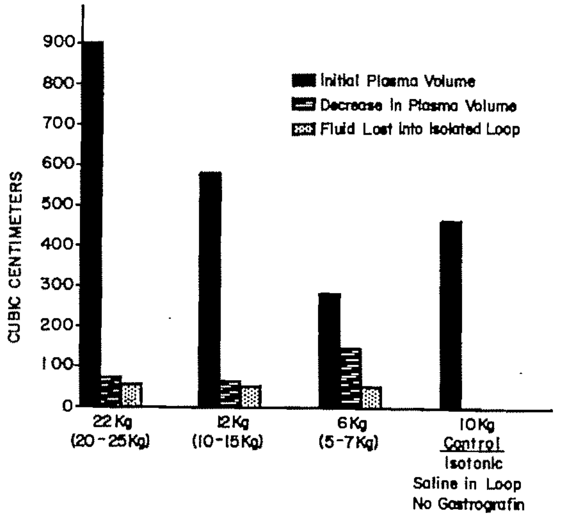

Fig. 8. The effect of gastrografin on the circulating plasma volume. The amount of fluid lost into the loops is independent of the size of the animal. The decrease in circulating plasma volume, however, depends on the initial circulating plasma volume. There was no change in circulating plasma volume when saline was instilled into the loop as a control.

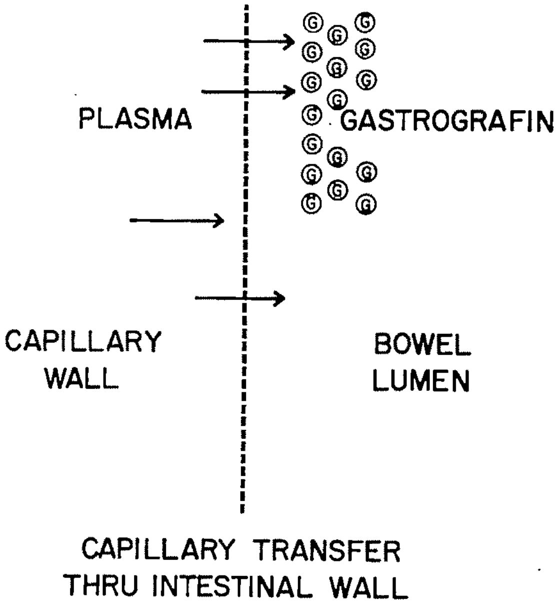

Fig. 9. Osmotic gradients produced by gastrografin. Gastrografin exerts a definitive osmotic force upon the contents of the vascular bed and draws fluid into the bowel lumen.

2. This force expressed as an osmotic gradient extracts a given quantity of fluid from the vascular compartment.

3. The volume of fluid transferred depends upon the length of time the medium is in contact with the bowel wall and the amount of gastrografin used.

4. The clinical effects seem to be related primarily to the ratio of the volume of fluid lost (secondary to the gastrografin osmotic effect) divided by the initial circulating plasma volume.

5. We, therefore, would expect that with small subjects, or those who have depressed circulating plasma volumes initially, the use of gastrografin might prove to be hazardous as has been borne out by several clinical and experimental observations.

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* * *

HEPATOPORTAL PNEUMATOSIS WITH MESENTERIC VENOUS THROMBOSIS IN AN INFANT*

REPORT OF A CASE

By JOSUE PAGAN-CARLO, M.D., *and* EDWARD H. DeMOUY, CAPT., U.S.A.F. (MC)†
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THE presence of gas in the intrahepatic portal venous system is recognizable on the plain roentgenogram of the abdomen and represents an ominous sign of impending death. All cases of gas in the portal venous channels reported in the literature have terminated fatally. The roentgenographic differentiation of air in the biliary tree from air in the portal system is important because there is an entirely different prognosis associated with each. Since Wolfe and Evans[4] in 1955 reported gas in the portal veins of 6 infants, there have been no other reports concerning this serious roentgenographic finding.

REPORT OF A CASE

This 12 day old white male infant did well for the first 9 days of life, but then developed severe diarrhea and vomiting. He was admitted to the hospital 48 hours following the onset of symptoms with a diagnosis of gastroenteritis and severe dehydration. On admission the abdomen was soft and the bowel sounds slightly hyperactive. Blood and umbilical stump cultures were reported later as negative for pathogens including gas-forming organisms. A program of rehydration was begun, but the infant developed a severely distended abdomen, and appeared acutely ill.

ROENTGEN FINDINGS

Roentgenographic examination of the abdomen revealed multiple severely distended loops of bowel, with fluid levels in the erect position and free air under the left side of the diaphragm (Fig. 1). A branching pattern of gas was demonstrable in the liver suggesting the presence of gas in the portal venous channels, extending into the hepatic veins, and inferior vena cava (Fig. 2).

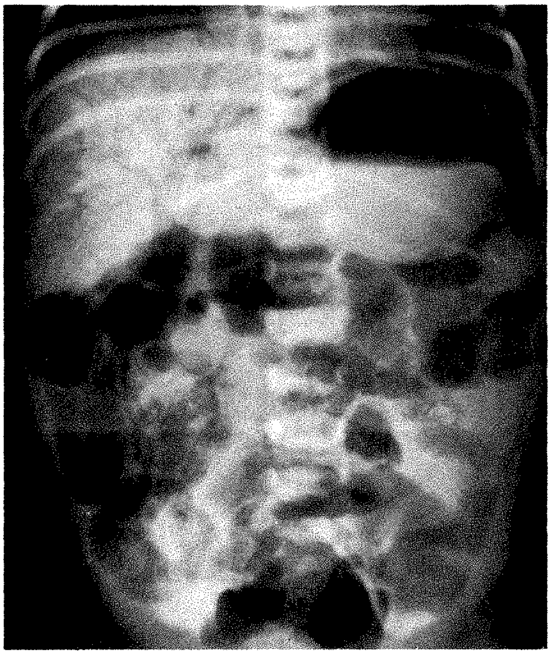

FIG. 1. Roentgenogram showing multiple severely distended loops of bowel with fluid levels and free air under the left side of the diaphragm.

OPERATIVE FINDINGS

The infant was explored. A perforation was found in the sigmoid colon, associated with a gangrenous descending colon and sigmoid. The mesenteric veins appeared like thick black cords indicating a venous thrombosis. As the mesentery was excised to resect the gangrenous loop of bowel, there was a feeling of crepitation suggesting the presence of air in the mesentery and blood vessels. The gangrenous loop was removed and a colostomy performed. The patient went into shock in the immediate postoperative period and expired 48 hours after admission.

NECROPSY FINDINGS

At autopsy the gangrenous process appeared to extend through the remaining colon and

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† This paper reflects the author's personal views and is not to be construed as a statement of official Air Force policy.

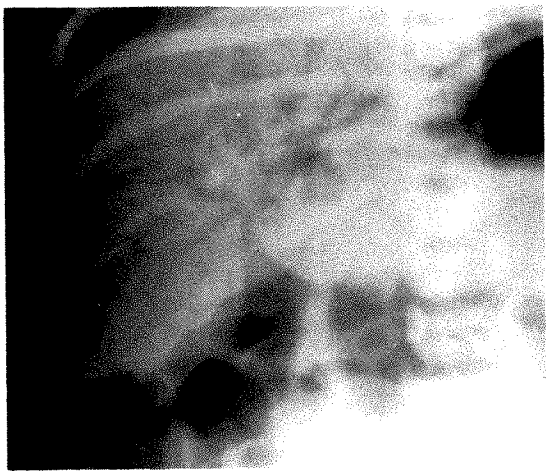

Fig. 2. Roentgenogram showing a branching pattern of gas in the liver.

terminal ileum. There was a recent mesenteric venous thrombosis. Gas erupted from the surface of the liver as it was cut. No biliary fistula was demonstrated. Cultures of the liver were negative for pathogens including gas-forming organisms. The final anatomic diagnosis was thrombosis of the mesenteric vein, secondary to severe dehydration. Microscopic examination of the liver revealed prominent congestion and mild intrahepatic cholangitis.

DISCUSSION

The presence of gas in the portal venous system can be readily differentiated from gas in the biliary tree after a careful observation of the gas patterns within the hepatic shadow. Sisk[2] established the roentgenographic crtieria that when the gas shadows extend in a branching pattern within the outermost 2 cm. of the hepatic margin, gas in the portal venous system is the presumptive diagnosis. It appears that gas in the portal venous channels of the liver appears to move cephalad with the blood flow,[3] while gas in the biliary tree appears to move caudally with the flow of bile outlining the main hepatic branches converging into the main hepatic bile duct; and sometimes outlining the gallbladder, depending on the location of the biliary fistula.

Several hypotheses have been advanced to explain the manner in which the gas enters the portal veins, of which two merit mentioning. The first, suggests that gas. under increased tension within the lumen of the bowel, the wall of which has been altered by impaired circulation due to severe dilatation or thrombosis, will move into the mesenteric veins and into the portal venous system. It is interesting to note that in all the reported infants there was a rather severe dilatation of the loops of bowel.[1,3] The second hypothesis suggests that the air or gas present in the venous radicles of the liver and mesentery may be due to a hematogenous dissemination and growth of gas-forming organisms. In all the cases reported by Wolfe and Evans,[4] positive blood cultures for *E. coli* were obtained.

Susman and Senturia[3] comment on the fact that all cases of gas in the portal venous system in adults were associated with mesenteric thrombosis. Alteration in the intestinal wall permeability due to vascular impairment may very well be the one important factor in allowing passage of intraluminal gas into the mesenteric veins. It has been demonstrated in the dog that as few as 5 cc. of air injected into the mesenteric vein are sufficient to outline the portal system of the left lobe of the liver.

It may also be noted that out of 15 cases including the case presently reported, 7 were infants. In all the cases there was a history either of severe diarrhea and/or vomiting, and abdominal distention. It may be reasonable to assume that the development of thrombosis involving the mesenteric vessels may be in some way related to the severe dehydration and hemoconcentration as a result of vomiting and/or diarrhea in these infants.

SUMMARY

Another case of gas in the portal venous system in infancy terminating fatally is presented. Differentiation of hepatoportal pneumatosis and gas in the biliary tree is possible; it is important from the clinical point of view and it can be established roentgenographically, although the former carries a rather hopeless prognosis.

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ANTENATAL ROENTGEN DIAGNOSIS OF INTRAPARTUM FETAL INFECTION IN PROLONGED LABOR*

By EUNG HO KIM, M.D.
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IN 1943, Douglas and Stander[2] described intrapartum infection following prolonged labor. They noted, on roentgenograms made shortly after the stillbirth, gas shadows in the intestine, lung, heart and great vessels of the infants. Davidson[1] also described a case of puerperal sepsis with roentgen manifestation of gas in the uterus and fetus. The occurrence of free gas in the vascular system of the fetus, in the peritoneal cavity or in the skull has been described by several authors as a sign of the intrauterine fetal death.[1,3,4,5,7] Recently, we observed gas in the chest, intestine and free peritoneal cavity of a fetus on an anteroposterior roentgenogram of the abdomen during pelvimetry studies. The purpose of this communication is to present a case in which an antenatal diagnosis of intrapartum infection was made. Gas shadows were demonstrated in the fetus and uterus following prolonged labor.

REPORT OF A CASE

The patient, a 27 year old Korean married woman, para 0, gravida 1, was admitted to another hospital on October 19, 1962 because of ruptured membranes and transferred to the Catholic Medical Center in labor at 5:30 A.M. on October 21, 1962. The pregnancy had been normal and October 10, 1962 was the expected birth date. Abdominal examination had revealed a single fetus and a cervix dilated to 3.5 cm. The fetal heart sounds could be heard until 11:00 P.M. A foul vaginal discharge was noted. Anteroposterior roentgenograms of the abdomen and pelvimetric roentgen studies were made on the following morning and showed a single fetus in cephalic presentation as well as gas shadows in the uterus, chest, intestine and free peritoneal cavity of the fetus (Fig. 1). A diagnosis of intrapartum fetal infection and fetal death was made. The patient's temperature rose to 99.5°F. and the vaginal discharge continued. A dead fetus was delivered on October 22 at 7:00 P.M. by the use of low forceps and an episiotomy after 96 hours of labor. Considerable extension of the episiotomy was required for the delivery of the large distended fetal abdomen. The stillborn infant weighted 3,450 gm. and the skull appeared to be macerated. The patient's temperature lasted for 2 days after delivery. She was treated with antibiotics and was discharged on October 28, 1962 in good condition.

DISCUSSION

Holm[3] stated that free gas in the fetus is the most common and the most important sign of intrauterine fetal death; however, there is some controversy as to the cause of gas formation in the fetus. Decomposition of certain blood elements,[1] gas embolism[5] and septicemia of gas forming organisms transferred from the blood of mother via the placental barrier to the fetus[4] have all been mentioned as possible causes. In 1957, Holm[3] reported that the factor responsible for the free gas in the fetus was due to the difference between the amount of chemically combined gas which was liberated when decomposition of the hemoglobin occurred during maceration and the comparatively small amount of gas which could be physically absorbed by the blood serum. Douglas and Stander[2] found fetal bacteremia in 85 stillborn infants, most of whom were born when there was intrapartum infection and following prolonged labor. The severity increased with the duration of labor. In their 2 cases, 1 was delivered following 105 hours of labor. The membranes had ruptured prematurely and the fetal heart sounds stopped 24 hours before delivery. In the other the delivery was spontaneous following 65 hours labor. The membranes in this case had also ruptured prematurely. In both, gas was demonstrated in the fetal intestines and lung or heart and great vessels. Davidson[1] described a case of prolonged labor with premature rupture of membranes in which gas shadows were noted in the uterus and fetus. Our case, delivered by forceps following 94 hours of labor and after the membranes had ruptured, showed gas in the uterus and fetal chest, intestine, free peritoneal cavity and biliary tree (Fig. 2). The origin of intrapartum infection is stated for the most part to be autogenous from the genital tract and carried to the fetus by various routes.[2] It is understandable that the rapidity with which intrapartum infection develops in the fetus is greatly enhanced by the early rupture of the membranes. Anaerobic streptococcus has been reported as the most common organism found in these stillborn infants.[1,2] This was true in the presently reported case. This anaerobic streptococcus (nonhemolytic) appears most likely of the normally present organisms found in the vagina to cause suppuration in traumatized tissues with resultant production of gas.[6] We feel that gas in the chest and intestine of a fetus in prolonged labor is a sign of intrapartum fetal infection, especially where the membranes have ruptured prematurely, and the presence of gas in a newborn infant is not a pathognomonic sign of postnatal breathing.

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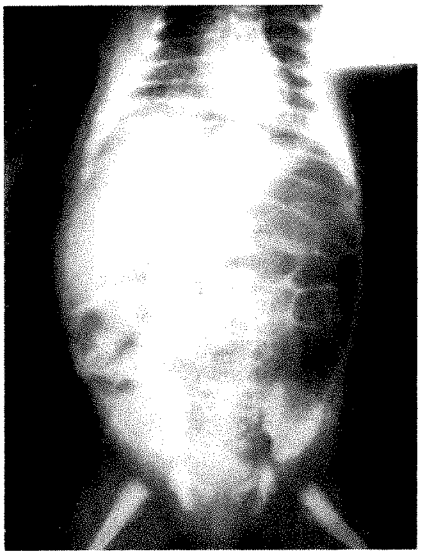

FIG. 2. Roentgenogram, taken immediately after the delivery, showing the gas shadows in the intestine, free peritoneal cavity, biliary tree and lung of the stillborn infant.

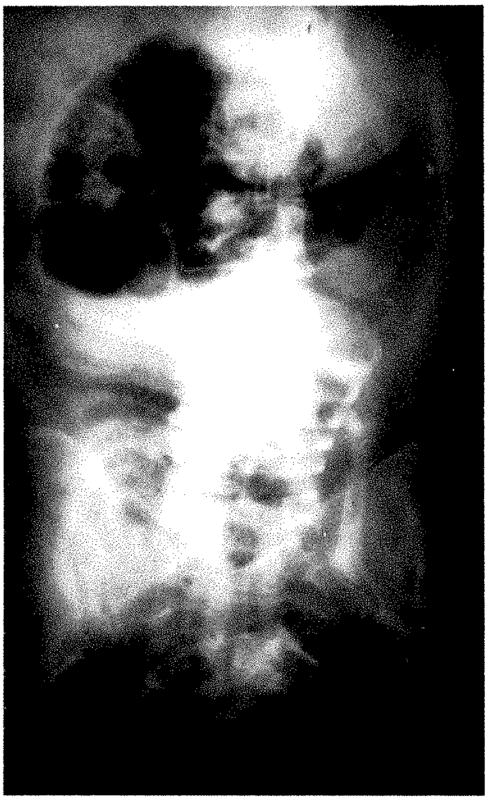

FIG. 1. Anteroposterior roentgenogram showing the single fetus in cephalic presentation and the gas shadows in the fetal intestine and chest and in the uterus.

SUMMARY

A case of intrapartum fetal infection due to anaerobic streptococcus is reported in which an antenatal diagnosis was made by the roentgenographic demonstration of gas in the uterus and fetus.

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EDITORIALS

SOCIETY FOR PEDIATRIC RADIOLOGY

THE articles in this issue of the JOURNAL are devoted to the radiologic study of the diseases of infants and children, and reflect the growing interest in pediatric radiology which has taken place during the past decade. A relatively few years ago in the brief evolution of radiology the idea of a radiologist limiting his practice to the pediatric age group would have been inconceivable. However, as both pediatrics and radiology became firmly established as vital specialties in the practice of medicine, the importance of utilizing radiologic procedures in the diagnosis of pediatric illnesses became increasingly apparent. This application was not as successful in the study of infants and children as in the older patient because of the necessity for rapid exposure times. Consequently, there resulted some delay in the correlation of many pediatric diseases and their roentgenographic manifestations. With time, improvement of X-ray equipment capable of short exposures gradually made it equally easy to study the infant and the adult. Interestingly, the difficulty of obtaining satisfactory quality roentgenograms in infants remains "like old wives' tales" to discourage many radiologists from accepting pediatric patients.

Pediatric radiology was conceived by the union of pediatrics and radiology, which just a short time ago were themselves in their infancy. It has been nourished, at times even coddled, and developed by a relatively few radiologists and pediatricians who recognized the importance of combining pediatrics and radiology into one group. The maturation of pediatric radiology into a distinct medical specialty has resulted from the establishment and development of pediatric hospitals, these institutions requiring specialized radiologic opinions which could be obtained only from those physicians having a knowledge of both pediatrics and radiology. The maturity of pediatric radiology as a significant specialty, embodying the general principles of radiology but with special attention to pediatrics, was acknowledged in 1958 by the formation of the Society for Pediatric Radiology.

The history of pediatric roentgenology in the United States from 1896 to 1956 has been vividly described by Dr. John Caffey in this JOURNAL in 1956 (*76*, 437). One has only to read this article and review the significant contributions which had been made up to that time by a rather small number of radiologists to realize that the following years have been extremely prolific in advancing both diagnostic and therapeutic pediatric radiology.

Through the organizational efforts of these few radiologists whose major interest was in the field of pediatric radiology, a meeting was held in 1958 in Washington, D. C., at which time the Society for Pediatric Radiology was founded. Dr. John Caffey was made an honorary counselor and Dr. Edward Neuhauser was elected the first president. There were approximately 35 individuals attending this meeting and soon thereafter a membership list was composed under the rules of the Constitution and By-laws listing 52 members. The purpose of the Society, as determined at the original meeting "is devoted to the problems associated with the practice of pediatric radiology" and to aid in the "education of members or others interested in these problems." It was decided that membership would be limited to those whose principal interest is in, or related to, the practice of pediatric radiology. Approximately 100 radiologists are now members of this Society.

Each subsequent meeting was greeted by renewed enthusiasm and by the addition of new members, but concomitant with this there developed, through necessity, a more official format. However, an informal atmosphere of "spirited debate" prevails and provides for interesting discussions of the scientific subjects which are presented. Subsequent meetings were held in Cincinnati in 1959, Atlantic City in 1960, Miami Beach in 1961, Washington, D. C. in 1962, and in Montreal, Canada in 1963. The next meeting will be held in Minneapolis, Minnesota this year. The respective presidents at these meetings were Dr. Fred Silverman (Children's Hospital, Cincinnati), Dr. John Holt (University of Michigan Hospital, Ann Arbor), Dr. Arthur Tucker (Babies and Children's Hospital, Cleveland, Ohio), Dr. John Hope (Children's Hospital, Philadelphia), Dr. Parker Allen (Children's Hospital, Denver), and Dr. Edward Singleton (Texas Children's Hospital, Houston). Dr. Richard Lester (Medical College of Virginia) served as secretary-treasurer from 1958 to 1962 at which time Dr. John L. Gwinn (Children's Hospital, Los Angeles) was elected to the position. Each meeting has been held on the Monday prior to the meeting of the American Roentgen Ray Society. This organization has been extremely hospitable and considerate in providing the facilities necessary for a meeting of radiologists, and the Society for Pediatric Radiology is grateful for its assistance.

The subject material at each of the meetings has been varied, both from a diagnostic and therapeutic aspect, covering a multitude of pediatric illnesses affecting the central nervous system, respiratory system, cardiovascular system, alimentary tract, gastrointestinal tract anomalies, the urinary tract and the skeletal system. Particular emphasis has been given to the evaluation of the lower urinary tract in infants and children, especially relating to vesicoureteral reflux. In reviewing the previous programs, it is also obvious that the skeletal dysplasias have been considered in detail not only in regard to etiologic speculations but also regarding the natural pathogenesis and inter-relationship of some of these anomalies. Congenital cardiac abnormalities, as well as neonatal pulmonary diseases, have also made up a significant number of the previous papers. Each of these subjects has received considerable attention in the pediatric literature and parallels the interest shown by pediatric radiologists. In the future years, many of the perplexing neonatal pulmonary conditions, particularly hyaline membrane disease, as well as the enigma of bone dysplasias, the significance of vesicoureteral reflux in the pediatric patient and a clearer understanding of chromosomal defects may well be more clearly understood as the result of the interest in these subjects by this group of radiologists.

In 1962 at the meeting in Washington, D. C., the Executive Committee of the Society for Pediatric Radiology was approached by Dr. LeFebvre and his associates, Dr. Sauvegrain and Dr. Faure of Paris, regarding the possibility of establishing an International Society for Pediatric Radiology. Their idea was enthusiastically accepted, and, through the exhaustive efforts of the French pediatric radiologists, the First International Reunion of Pediatric Radiologists was held in Paris, in May 1963.

Because of the rapid strides in the field of Pediatric Radiology and because of the number of enthusiastic, energetic and competent young physicians interested in this field, the future of this specialty is exciting and one may anticipate many beneficial results to the sick infant and child through both diagnostic and therapeutic radiology.

Edward B. Singleton, M.D.

Director, Department of Radiology
Texas Children's Hospital
Houston, Texas

IN MEMORIAM
ARTHUR U. DESJARDINS
1884-1964

DR. ARTHUR U. DESJARDINS, head of the Section of Therapeutic Radiology of the Mayo Clinic from 1920 to 1948, and a pioneer figure in the development of medical work with x-rays in the United States, died in the Community Hospital in Damariscotta, Maine, on January 15, 1964 of the effects of coronary arterial disease. Dr. Desjardins retired from the Mayo Clinic in 1949 and moved with Mrs. Desjardins to Damariscotta, near Walpole.

Dr. Desjardins was born in Waterville, Maine, on May 6, 1884, the son of Sarah Marie Mercier Desjardins and Samuel Desjardins. He studied at Montreal College from 1898 to 1900 and Saint Joseph's College in Three Rivers, Canada, in 1900 and 1901. In 1912 he received the degree of Doctor of medicine from the University of Pennsylvania; in 1913 and 1914 he was in charge of the Fairfield Tuberculosis Sanatorium in Fairfield, Maine.

In 1914 Dr. Desjardins went to France, where he was associated with the American Hospital in Paris. He also was assistant surgeon to American Ambulance in Paris. In 1915 and 1916 he was first assitant surgeon to Dr. Joseph Blake at a military hospital in Ris Orangis, France.

On February 1, 1917, Dr. Desjardins was appointed a fellow in surgery in the Mayo Foundation, but he had been commissioned a captain in the Medical Reserve Corps of the Army in June of that year, and was ordered to active duty in August. He served as pathologist to various medical units in France, and was commanding officer of the Third Army Laboratory in Coblenz, Germany, in 1919. He was released to civilian life in July, 1919, with the grade of major. He continued his military interests in the Officers Reserve Corps, in which he attained the grade of colonel in 1935.

Dr. Desjardins resumed his fellowship at the Mayo Foundation on January 1, 1920, but changed his major sequence to roentgenology. In the summer of that year, he studied radiologic physics at the University of Cambridge, England, and in October of that year he was made head of the Section of Therapeutic Radiology of the Mayo Clinic, a post he held until July 1, 1948, when he became a senior consultant. He retired from active practice at the Mayo Clinic on October 1, 1949.

Dr. Desjardins received the degree of master of science in radiology from the University of Minnesota in 1924. A year later he was appointed an instructor in radiology in the Mayo Foundation, Graduate School, University of Minnesota, and he was advanced to assistant professor in 1928, associate professor in 1933 and professor in 1936. In 1934 he was certified as a radiologist by the American Board of Radiology.

Dr. Desjardins, at the beginning of his career, was interested chiefly in surgery; shortly after he returned from service in World War I, he changed his major interest to therapeutic radiology, and in this field he achieved nation-wide recognition as an authority. He contributed more than 100 papers to the medical literature, some of them in French, which he spoke and wrote fluently. He was a member of the Council on Physical Medicine of the American Medical Association for a number of years, and he also was a member of the Council on Industrial Health of that association. In 1939 he served as a consultant to the Federal Communications Commission on the problem of radio interference. He was recognized as being exceptionally proficient in photography, and was an early worker in color photography. His photographs received widespread attention and admiration.

Dr. Desjardins was a fellow of the American College of Physicians and a member of the Southern Minnesota Medical Association, the Clinical Congress of Internal Medicine, the Radiological Society of North America, the American Medical Association, the American Roentgen Ray Society, the American Radium Society, the Alumni Association of the Mayo Foundation and the Society of the Sigma Xi. He was an honorary member of the Roentgen Society of England. In 1950 the University of Minnesota conferred upon him a certificate of merit in appreciation of his long tenure of service to the university as a member of the faculty.

After he moved to Damariscotta in 1949, Dr. Desjardins became a consultant in radiology to its Community Hospital, and was a prime force in efforts to raise funds for the purchase of x-ray equipment for the hospital. He took an active part in civic affairs in both Damariscotta and Walpole.

Dr. Desjardins was married to Miss Marie Laure Jeanne d'Argy on January 30, 1913. She died on September 14, 1924. On April 10, 1926, he was married to Miss Helen Beatrice Hardy, of Rochester. Dr. and Mrs. Desjardins had three children: Adrienne Aymard (Mrs. Edward Ackerman, of Washington, D. C., currently living in Switzerland); Paul Arnault of New York City; and Vincent (deceased).

James Eckman, M.D.

NEWS ITEMS

LA PRENSA MEDICA ARGENTINA

La Prensa Médica Argentina, considered the most important Journal of Medicine in South America, celebrates in 1964 the Fiftieth Anniversary of its foundation.

The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, on whose pages abstracts of articles by illustrious radiologic contributors to the *Prensa méd.* have appeared for many years, extends its most sincere congratulations and very best wishes on this festive occasion.

TWENTY-FIFTH ANNUAL CONGRESS OF THE BRITISH INSTITUTE OF RADIOLOGY

The Twenty-fifth Annual Congress and Exhibition of The British Institute of Radiology will be held April 22–24, 1964 at the Central Hall & Church House, Westminster, London, England.

An outstanding Scientific Program has been arranged. The topics to be presented are in the format of symposia and they include the following subjects: April 22nd—The blood Supply of Tumors; April 23rd—Factors Affecting the Results of Radiotherapy; Dosimetry in Radiotherapy; Tropical Radiology; and April 24th—Electron-Spin Resonance in Radiation Research; Radiology of Iatrogenic Lesions; and The New Code of Practice for Radiology.

The Silvanus Thompson Memorial Lecture will be delivered on April 22, 6:00 P.M., by Dr. M. F. Perutz, C.B.E., F.R.S. Its title is X-Ray Analysis of Proteins.

The Scientific Exhibition will consist of instruments, models, diagrams, charts and films illustrating work in the fields of Radiodiagnosis, Radiotherapy, Radiobiology and Physics.

The Council of the Institute cordially invites radiologists from overseas to attend this meeting. Fur further information, registration forms and details of hotel accommodations please write to R. D. Hoare, MB., BS., DMRD., Honorary Medical Secretary of the Institute, 32 Welbeck Street, London, W.1., England.

VI$^{\text{ème}}$ CONGRÈS DES MÉDECINS ÉLECTRO-RADIOLOGISTES DE CULTURE LATINE

The Sixth Congress of Electro-radiologic Physicians of Latin Culture will be held in Brussels, Belgium, July 13–18, 1964, with Professor Leroux of Liège as President.

The topics to be discussed include: (1) *Section of Diagnosis:* lymphography, cineradiology of stomach, radiology of organs of the small pelvis and retrogastric region. (2) *Section of Radiobiology:* factors of radiosensitivity and radioresistance. (3) *Section of Radiotherapy:* association of radiotherapy and chemotherapy in radioresistant cancers; techniques and results. Treatment of sarcomas of soft parts by ionizing radiations. Technical problems in connection with supervoltage installations. (4) *Section of Nuclear Medicine:* renal studies by means of radioactive isotopes; treatment of hemolymphopathies with radioactive isotopes. (5) *Section of Electrology:* involvement of the motor neurons in cervicoarthrotic radiculo-myelopathies. (6) *Professional Organization:* the status of radiology in relation to present legislation.

For further information please contact Dr. P. De Plaen, 256, Chaussée de Wavre, Heverle-Louvain, Belgium.

SPRING CONFERENCE OF THE NEW YORK ROENTGEN SOCIETY

The Spring Conference of the New York Roentgen Society (formerly The Eastern Conference of Radiologists) will be held April 23–25, 1964, at the Waldorf-Astoria Hotel, New York City.

The highlights of the Scientific Program, under the direction of Dr. William B. Seaman, Professor of Radiology, Columbia-Presbyterian Medical Center, are: (1)

Annual Ross Golden Lecture by Dr. Harold O. Peterson, Professor of Radiology, University of Minnesota School of Medicine; (2) One Scientific Session in honor of Dr. Golden by a group of his former residents; (3) Refresher Courses under the direction of several leading radiologists; and (4) Selected papers on topics of current interest.

The 1964 World's Fair opens on April 22, 1964.

The General Chairman of the Conference is Dr. Albert A. Dunn, The Roosevelt Hospital, 428 West 58th Street, New York 19, New York.

COURSE IN RADIOLOGY OF THE HEART AT INDIANA UNIVERSITY

The Department of Radiology of Indiana University School of Medicine announces a postgraduate course in Radiology of the Heart to be given April 8–11, 1964, at the Medical Center in Indianapolis.

The course is planned primarily for the general radiologist but is open to all physicians having an interest in this field. Presentations will consist of lectures, panel discussions, film interpretation conferences, and exhibits correlating the radiologic, pathologic, and physiologic aspects of various cardiac conditions encountered in clinical practice.

The course will be presented by members of the faculty of Indiana University School of Medicine and a guest faculty of distinguished radiologists from various parts of the country, who are well known for their accomplishments in this field.

The subjects for discussion have been arranged so that each day is devoted to one or two major subdivisions of the field, thus facilitating a more comprehensive evaluation of lesions of similar origin, as well as those producing similar roentgen findings.

Registration forms and further information regarding this course may be obtained by writing the Director of Postgraduate Medical Education, Indiana University School of Medicine, Indianapolis 7, Indiana.

SIXTEENTH ANNUAL FREEDMAN LECTURES

Dr. Bernard S. Wolf, Chairman of the Department of Radiology of Mount Sinai Hospital and Associate Clinical Professor of Radiology at Columbia University, New York City, will present the University of Cincinnati Medical Center's Sixteenth Annual Freedman Lectures Saturday and Sunday, April 4 and 5, 1964, at the Cincinnati General Hospital.

Additional information can be obtained from Dr. Jay Crittenden, Department of Radiology, Cincinnati General Hospital, Cincinnati 29, Ohio.

BOOK REVIEW

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

Tumors of the Chest. By Thomas J. Kinsella, M.D., Clinical Professor of Surgery, University of Minnesota; Senior Consultant, Thoracic Surgery, U. S. Veteran's Bureau Faculty, Fort Snelling, Minnesota. Cloth. Pp. 145, with many illustrations. Price, $9.50. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1963.

This small atlas attempts to cover the vast subject of chest tumors in 145 pages. The book is well organized into 18 chapters, each of which is brief but full of substance. It is readily apparent when reading the book that the author has had a great deal of experience in thoracic surgery. There are many well reproduced illustrations and a number of references for each subject covered.

This book can be recommended to one who desires to acquire a general knowledge of tumors of the chest, but he must then resort to the references for more details. It is truly what the author intended it to be, an atlas.

Francis S. Gerbasi, M.D., F.A.C.S.

BOOKS RECEIVED

Progress in Medical Radioisotope Scanning. Proceedings of a Symposium at the Medical Division of the Oak Ridge Institute of Nuclear Studies, October 22–26, 1962. Edited by Ralph M. Kniseley, M.D., Gould A. Andrews, M.D., and C. Craig Harris, M.S., with Elizabeth B. Anderson, M.D., as Technical Editor. Paper. Pp. 540, with many illustrations. Price, $3.50. Office of Technical Services, U. S. Department of Commerce, Washington, D. C., 20230, 1963.

A Study Guide for Student X-Ray Technicians. By Joyce Oliphant, B.Sc., R.T. (ARXT), Chief Instructor, School of X-Ray Technology, Department of Radiology, Macon Hospital, Macon, Georgia. Cloth. Pp. 157. Price, $5.50. Charles C Thomas, Publisher, Springfield, Ill., 1963.

Annual Review of Nuclear Science. Volume 13. Edited by Emilio Segrè, University of California; Associate Editors, Gerhart Friedlander, Brookhaven National Laboratory, and H. Pierre Noyes, Stanford University. Cloth. Pp. 590, with some figures. Price, $8.50. Annual Reviews, Inc., 231 Grant Avenue, Palo Alto, Calif., 1963.

Atomic Energy Encyclopedia in the Life Sciences. Edited by Charles Wesley Shilling, M.D., D.Sc., Consultant to United States Atomic Energy Commission; Deputy Director, Division of Biology and Medicine, United States Atomic Energy Commission, 1955–1960; with the assistance of Miriam Teed Shilling, M.A. Prepared under the auspices of the Division of Technical Information, United States Atomic Energy Commission. Cloth. Pp. 474, with many illustrations. Price, $10.50. W. B. Saunders Company, Philadelphia, Pa., 1964.

A Handbook of Radiography. By John A. Ross, M.A., F.R.C.P., D.M.R.E., Consultant Radiologist, David Lewis Northern Hospital; Regional Hospital Board, Liverpool; Assistant Lecturer in Radiology, Liverpool University; and R. W. Galloway, M.D., F.F.R., D.M.R.D., D.R.C.O.G., Consultant Radiologist, Regional Hospital Board and University Research Assistant, Liverpool; with a Chapter on Neuro-Radiology by R. G. Reid, M.B., D.M.R.E., F.F.R., Consultant Radiologist, Manchester Royal Infirmary. Third edition. Cloth. Pp. 220, with 109 illustrations. Price, $7.00. J. B. Lippincott Company, East Washington Square, Philadelphia 5, Pa., 1963.

Cancer: Progress Volume 1963. Edited by Ronald W. Raven, O.B.E.(MIL.), T.D., F.R.C.S., Joint Lecturer in Surgery, Westminster Medical School, University of London; Surgeon, Westminster Hospital; Senior Surgeon, The Royal Marsden Hospital and Institute of Cancer Research, Royal Cancer Hospital, London; Surgeon, The French Hospital, London. Cloth. Pp. 268, with some illustrations. Price, $12.00. Butterworth Inc., 7235 Wisconsin Avenue, Washington 14, D.C., 1963.

The Radiologic Clinics of North America. Symposium on Pediatric Radiology. Volume 1, Number 3, John A. Kirkpatrick, Jr., M.D., Guest Editor. Cloth. Pp. 647, with many illustrations. W. B. Saunders Company, Philadelphia, Pa., 1963.

Strahlenpathologie der Zelle: Beiträge zur Zyto- und Histopathologie der Strahlenwirkung. Herausgegeben von Prof. Dr. med. Eberhard Scherer, Direktor des Röntgen- und Strahleninstituts der Städtischen Krankenanstalten Essen; Klinikum der Universität Münster; and Priv.-Doz. Dr. med. Hans-Stephan Stender, Oberarzt an der Strahlenklinik und -poliklinik der Universität Marburg/Lahn. Cloth. Pp. 390, with many illustrations. Price, Ganzleinen DM 90. Georg Thieme Verlag, Postfach 732, Herdweg 63, 7000 Stuttgart 1, Germany. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N.Y., 1963.

ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

NECK AND CHEST

HAN, SANG Y., RUDOLPH, ARNOLD J., and TENG, CHING T. Pneumomediastinum in infancy. *J. Pediat.*, May, 1963, *62*, 754–761. (From: Jefferson Davis Hospital, Houston 3, Tex.)

Pneumomediastinum in infants is frequently associated with active resuscitation, obstruction of the respiratory tract with increased intra-alveolar pressure, or it may occur spontaneously without any demonstrable cause. If routine chest roentgenograms were taken in the neonatal period, the true incidence of the condition would probably be much higher than is now recognized as many of these infants are entirely asymptomatic.

The author presents 6 cases of pneumomediastinum in infants seen over a period of 10 months. Two cases were preceded by tracheostomy and 3 cases were associated with pneumothorax. Roentgenograms with line tracings are presented to demonstrate that the separation of the thymic shadow from the heart and great vessels is the most important roentgenologic sign of pneumomediastinum in this age group. The lateral projection is not forgotten and it is pointed out that the air may be loculated immediately posterior to the sternum. The clinical manifestations of respiratory difficulty and circulatory embarrassment are dependent upon the extent of the pneumomediastinum and pneumothorax.—*John L. Gwinn, M.D.*

JOHNSON, JOHN R., and ZINTEL, HAROLD A. Pancreatic calcification and cancer of the pancreas. *Surg., Gynec. & Obst.*, Nov., 1963, *117*, 585–588. (From: Surgical Service, St. Luke's Hospital, New York, N.Y.)

In the past, calcification of the pancreas has been considered evidence of a nonmalignant pancreatic lesion. More recent reports have suggested a higher incidence of pancreatic carcinoma in persons with chronic pancreatitis than in the general population, particularly if there is associated calcification.

Sixty-four patients with a confirmed diagnosis of chronic pancreatitis and 113 patients with a histologic diagnosis of cancer of the pancreas were studied. Thirty-eight per cent of the patients with chronic pancreatitis showed roentgenologic or surgical evidence of calcification, with alcoholism and gallbladder disease as the primary inciting causes.

Not one of the 113 patients with carcinoma had a well documented diagnosis of chronic pancreatitis. Also, not one of the patients with chronic pancreatitis had associated carcinoma. This contrasts with a review of the English literature which shows 24 patients with pancreatic cancer among 677 with pancreatic calcification, an incidence of 3.6 per cent. Isolated reports have placed this value as high as 10 to 20 per cent and have suggested exploratory laparotomy whenever pancreatic calcification is discovered. In view of the present findings, this procedure is probably unwarranted.—*David P. Corbett, M.D.*

GYNECOLOGY AND OBSTETRICS

OGAWA, G., and KONNO, A. A new method of outlet pelvimetry. *Am. J. Obst. & Gynec.*, July 15, 1963, *86*, 706–807. (From: Department of Obstetrics and Gynecology, Hokkaido University, School of Medicine, Hokkaido, Japan.)

The fetal head in its descent impinges on the posterior edge of the pubic arch, or on the tip of the sacrum. In cases in which the pubic arch is narrow, the head will be pressed firmly against either the inner border of the narrowed pubic arch or the tip of the sacrum.

These "touch points of the fetal head on the pubic arch" may be used to define the final and narrowest passage at the outlet. The actual available space at this level, as delimited by these three points, is the key to the prediction of the course of labor. This available space was designated as the true space of outlet and is based on a circle drawn through the three touch points.

Where the subpubic angle is wide, the head will descend on a regular course, but when the subpubis is too narrow, the head will impinge on the rami of the narrowed angle, and as a result it will swerve back and downward far from the normal course. In other words, the head may be forced to turn and make a detour on the fulcrum of the impinging points on the descending pubic rami.

Two roentgenograms, a lateral view and a pubic arch view, are obtained in all cases in which a contracted outlet is suspected. The lateral roentgenogram is essentially that of Thoms' view and is obtained by having the patient stand upright with a centimeter scale inserted between the thighs. The pubic arch roentgenogram is taken with the use of Treptow's technique, the patient sitting with the cassette beneath her and stooping forward as far as possible while the tube is centered over the tuberosities, at a tube-film distance of 100 cm.

In the abstractor's opinion the method of measuring is quite fully described but seems rather cumbersome. The points selected to calculate the "true outlet space" are easily theorized and demonstrable on a dry skeleton. The application in an active first-stage-labor patient would, however, seem unduly difficult for the information to be gained.—*Eugene J. McDonald, M.D.*

FAINSTAT, THEODORE. "Physiological hydroureter" of pregnancy in a four-legged animal.

Am. J. Obst. & Gynec., Oct. 15, 1963, *87*, 486–492. (From: Department of Obstetrics and Gynecology, Harvard Medical School, and the Biological Laboratories, Harvard University, Boston, Mass.)

The author performed excretory urography in a series of rats late in pregnancy and compared the size of the ureters in these animals with those of a control series of nonpregnant rats. He found that the average diameter of the upper third of the ureter in the pregnant animals was 52 per cent larger than in the control group.

As there are no known obstructive factors in this type of quadriped in the urinary tract even late in pregnancy, it is concluded that this dilatation is entirely caused by physiologic hormonal changes of pregnancy. In mammals, where a more erect posture or biped gait is common, ureteral dilatation in pregnancy may be partially due to obstructive factors as well.—*Arthur E. Childe, M.D.*

Hutch, John A., Ayres, Robert D., and Noll, Leland E. Vesicoureteral reflux as cause of pyelonephritis of pregnancy. *Am. J. Obst. & Gynec.*, Oct. 15, 1963, *87*, 478–485. (From: Division of Urology, University of California School of Medicine, San Francisco, and Departments of Urology and Obstetrics and Gynecology, Contra Costa County Hospital, Martinez, Calif.)

Almost all pregnant women develop dilatation of the urinary collecting system from the pelvic brim upward, and in about 2 per cent infection of this static urine occurs with a severe type of pyelonephritis.

The relationship between pyelonephritis of pregnancy and pyelonephritis of childhood is firmly established and it is recognized that women who enter pregnancy with such a history have a much greater than average chance of having their pregnancy complicated by pyelonephritis.

The accumulating evidence that pyelonephritis in both children and adults is caused by incompetence of the ureterovesical valve suggests that pyelonephritis of pregnancy may also be caused by vesicoureteral reflux. There is reason to suspect that in pregnancy the infecting organisms gain entrance through the bladder and whether or not the kidneys become involved depends upon the competence of the ureterovesical valves.

The authors studied a group of 12 pregnant patients suffering from pyelonephritis. To avoid excessive irradiation only two roentgenograms were made, one with the bladder filled with contrast medium and the other during voiding. In spite of these limitations ureteral reflux was demonstrated in 5 instances. They also analysed a group of 23 adult women who had recurring or chronic pyelonephritis with proved ureteral reflux and found that 54 per cent suffered from pyelonephritis of pregnancy.—*Arthur E. Childe, M.D.*

Weineerg, Arthur, Shapiro, Gerald, and Bruhn, Donald F. Isotopic placentography: an evaluation of its accuracy and safety. *Am. J. Obst. & Gynec.*, Sept. 15, 1963, *87*, 203–209. (Address: 1462 Greenport Road, Far Rockaway 91, N.Y.)

The roentgenologic determination of the placental site by soft tissue, contrast, or displacement techniques is about 95 per cent accurate after the 35th week of gestation. However, from the 28th to the 35th week, that is in the first half of the last trimester when the condition most requires aid, the results are not as accurate.

Localization of the placental site by radioactive isotopes provides a method of immediate bedside study with relatively simple equipment. The procedure is useful throughout the entire third trimester regardless of maternal obesity, fetal presentation, hydramnios, multiple pregnancy, or pelvic tumors.

In the present procedure, 5 mc of radioactive iodinated human serum albumen is injected intravenously. After allowing 10 minutes for mixing in the bloodstream, radioactivity measurements are made over the abdominal region and heart with a shielded straight bore scintillation counter positioned normally to the surface of the skin. The counts over the fundus of the uterus are usually about one half to two thirds of those over the heart. The counts are entered on a special chart showing the heart, 12 areas of the uterus, and a right and left lateral flank area. When the placenta is situated on the anterior wall of the uterus, the site is indicated by a region where the counting rate is considerably more than that over the remainder of the uterus, and is almost equal to the rate over the heart. The counting rate is usually lower over the lower portion of the uterus than over the fundus. Where this decrease does not occur, it is indicative of a placenta in previa position.

The whole body and gonadal radiation to mother and fetus is minimal (1 per cent) in comparison to that received in 2 film roentgen placentography.

If a thyroid blocking agent is used, the absorbed dose delivered to the fetal thyroid will be well within the values as listed by the Federal Radiation Council and about 1 per cent of the dose delivered by conventional roentgenographic techniques.—*Eugene J. McDonald, M.D.*

Bossart, H., and Delaloye, B. La placentographie par injection de sérumalbumine humaine marquée à l'iode 132: technique de localisation placentaire. (Placentography by the injection of human serum albumine tagged with I^{132}: technique of placental localization.) *Schweiz. med. Wchnschr.*, July, 1963, *93*, 958–962. (From: Clinique Universitaire d'Obstétrique et de Gynécologie, Lausanne, Switzerland.)

After study of the different techniques of placental localization, the authors chose the isotopic one, using radioiodinated serum albumine labelled with I^{132}. They stress the very great advantages of I^{132} over I^{131}, due to the very short half-life of I^{132} (2 hr. 26 min.). With this isotope, the fetal gonadal dose is reduced to 7 millirads and the fetal thyroid dose to 130 millirads.

The technique consists of an intravenous injection of $RI^{132}SA$, followed by radioactive mapping of the abdomen by means of a scintillation counter.

Three interesting cases, with one scintigram, are reported.—*Étienne Lebel, M.D.*

McLain, Clarence R., Jr. Amniography studies of the gastrointestinal motility of the human fetus. *Am. J. Obst. & Gynec.*, Aug. 15, 1963, *86*, 1079–1087. (From: Departments of Obstetrics and Gynecology, Indiana University Medical Center, and the Marion County General Hospital, Indianapolis, Ind.)

Many investigators have demonstrated that gastrointestinal motility occurs *in utero* in animals and humans. It is reasonable to propose that the gastrointestinal system has a very dynamic and essential function during intra-uterine life, and that pathologic states can alter normal function. The purpose of the present study was to determine the gastrointestinal motility in the human fetus at different periods of gestation in normal and abnormal pregnancies.

The procedure consisted of opacifying the amniotic fluid in the pregnant uterus with a suitable contrast medium in order to delineate the uterine cavity and to study certain aspects of maternal and fetal physiology. The gastrointestinal motility of the fetus was studied in 33 normal pregnancies, varying from 24 to 40 weeks' gestation and in 17 abnormal pregnancies with erythroblastosis, toxemia, hydramnios, diabetes, chronic renal disease, sickle-cell anemia, and premature separation of the placenta.

A volume of amniotic fluid was removed equal to the amount of contrast medium injected. Thirty to forty cubic centimeters of medium was the usual dose. This varied depending on estimates of amniotic fluid volume. In subjects with hydramnios larger amounts of amniotic fluid were removed and approximately 50.0 cc. of medium were injected because of the increased volume of amniotic fluid.

In this study there was no incidence of premature labor caused by the procedure. Some of the patients were delivered prematurely; however, in each case there was bleeding or other causes which contributed to the onset of labor. There was no trauma to either fetus or mother. The infants were followed through the neonatal period and no ill effects due to the procedure were observed.

There was an increase in gastrointestinal motility and in rate of progress through the gastrointestinal tract as pregnancy advanced. In the cases of hydramnios studied there was a decrease in the rate of swallowing of the fetus, and a decrease in gastrointestinal motility. This may be an etiologic factor in the development of hydramnios. In the 2 diabetic patients studied, the gastrointestinal motility was decreased with the development of hydramnios.—*Eugene J. McDonald, M.D.*

Genitourinary System

Harrison, A. R., and Ghose, R. R. Nephrocalcinosis. *Proc. Roy. Soc. Med.*, Oct., 1963, *56*, 925–927. (From: St. Philip's Hospital, London, England.)

Nephrocalcinosis is defined as diffuse calcification in the renal parenchyma which is visible on ordinary roentgenograms. Usually it takes the form of multiple discrete deposits of calcium salts in the medullary region of one or both kidneys. Only in the medullary sponge kidney is the appearance characteristic.

Forty-six cases of nephrocalcinosis were seen in the previous 7 year period in the Metabolic Department of St. Philip's Hospital. Thirty-one cases were secondary to primary hyperparathyroidism, renal tubular acidosis and medullary sponge kidney, in approximately equal numbers. Four cases were due to calciuria, 2 to pyelonephritis and in 9 cases no cause was found.

A short discussion of the clinicopathologic features of the 3 leading causes is given.—*Donald S. Linton, Jr., M.D.*

Phillips, D. E. H. The percutaneous aspiration of renal cysts. *Proc. Roy. Soc. Med.*, Oct., 1963, *56*, 928–930. (From: St. Paul's Hospital, London, England.)

The author describes his technique of percutaneous aspiration of renal cysts in a series of 12 patients.

Under television-fluoroscopic control a direct needle approach posteriorly is used; the cyst contents are aspirated and replaced by a contrast medium. Analysis of the cyst fluid permits differentiation between benign and malignant renal cysts. A "dry tap" is presumptive evidence of a solid renal carcinoma.

The patients are limited to those in whom the previous clinical and roentgenographic examinations suggested the presence of a benign cyst. In spite of this, 3 of the 12 cases proved to have renal carcinoma. Prompt surgical treatment is undertaken if a "dry tap" results.

The author feels that this technique is more reliable than angiography in the diagnosis of avascular tumors and in cystic carcinomas.—*Donald S. Linton, Jr., M.D.*

Tarabulcy, Edward Z. The radiographic aspect of urogenital schistosomiasis (bilharziasis). *J. Urol.*, Oct., 1963, *90*, 470–475. (From: Department of Surgery, Cornell University Medical College: Second Division, Surgery [Urology], Bellevue Hospital, New York, N.Y.)

Schistosomiasis is rarely seen in this country. The disease is caused by blood flukes which gain entrance through the skin and eventually reach the hepatoportal system, developing into male and female adult worms. These worms then leave the liver to lay their eggs at the outlets of the alimentary and urinary tract.

From a roentgenographic standpoint, three urogenital organs are of importance, namely the bladder, ureter, and seminal vesicles.

The bladder is the organ most frequently and severely involved. The organisms produce a thin linear calcification of the vesical wall which is referred to as an "eggshell" calcification. In the presence of associated malignant growth of the bladder, areas of calcification may be missing. Bladder stones and sometimes calcified polyps are a frequent complication.

The ureter infested with bilharziasis shows calcification which is most marked in its lower third and secondly at the level of the third lumbar vertebra. In advanced cases, the entire length of the ureter is calcified. In the later stages of the disease, fibrosis and stricture of the ureter not infrequently result in the formation of urinary calculi and calcified polyps. Filling defects which may resemble air bubbles seen on excretory urograms are present in instances where ureteritis cystica has developed.

The seminal vesicles, when involved, become calcified and present a characteristic appearance. Prostatic calcification is uncommon and the kidney is rarely affected primarily. Renal hydronephrosis may be the result of ureteral stricture.

Eleven figures illustrate the findings presented by the author.—*George W. Chamberlin, M.D.*

Hirschfeld, Robert L. Nephro-urography in the diagnosis of hypertension: a preliminary study. *South. M. J.*, Sept., 1963, *56*, 975–980. (From: Department of Radiology, Veterans Administration Hospital, Oklahoma City, Okla.)

The author alters the usual urographic procedure done with 30–50 cc. of ditriokon or hypaque 50 per cent by injecting the medium rapidly (4 to 8 seconds) with a No. 18 gauge needle. Selective 10×12 inch roentgenograms of the renal area are made at 1 and 3 minutes, plus essential later roentgenograms.

Investigations were carried out to note the benefit of rehydration in hypertension; 18 to 24 ounces of water were given following the 15 minute roentgenogram and another roentgenogram was made 15 to 30 minutes later. Clearance of the contrast medium did not occur in the diseased kidney of hypertensive patients.

The early phase roentgenograms or nephro-urography have been of great help in the elucidation of the site of the renal abnormality, since on routine study the pelvocalyceal system of the abnormal kidney may be visualized as equal, increased or decreased radiopacity when compared with the opposite kidney. Accurate appraisal of renal size, contour and renal function can be made.—*John H. Harris, M.D.*

Brooks, R. Teryl, Jr., Dettman, Prentiss M., and Galuszka, Albin A. Renal scans in urologic diagnosis using neohydrin Hg-203. *J. Urol.*, July, 1963, *90*, 107–112. (From: Urological Service and the Radioisotope Laboratory, United States Naval Hospital, National Naval Medical Center, Bethesda, Md.)

This is a preliminary report of 120 patients who were subjected to renal scan after the intravenous injection of 50 μc of neohydrin Hg^{203}. With the patient in the prone position, the usual dot scan and photo recording scan were made approximately 1 to 3 hours following the intravenous injection of the radioactive mercury.

Six brief case histories are included in this article. It is believed that neohydrin Hg^{203} scan is a satisfactory technique particularly in the following 4 groups of patients: (1) those who are sensitive to iodine; (2) patients with nonfunctioning kidney on excretory urography; (3) hypertensive patients with suspected renal artery disease; and (4) patients who have a mass lesion involving the kidney.

The scan has been shown to be nonspecific in depicting lesions of the kidney but is a valuable adjunct to pyelography and arteriography in the study of renal disease.

The renal scan was not accurate for a small number of patients who had extrinsic renal masses and was found to be of no significant value for patients with medical renal diseases.

Four tables and 7 composite figures are included to illustrate the points made by the authors.—*George W. Chamberlin, M.D.*

Dore, Earl K., Taplin, George V., and Johnson, De Lores E. Current interpretation of the sodium iodohippurate I^{131} renocystogram. *J.A.M.A.*, Sept. 21, 1963, *185*, 925–932. (Address: Dr. E. K. Dore, 900 Veteran Avenue, Los Angeles 24, Calif.)

New terminology for the renogram's 3 segments is recommended; *i.e.*, tracer appearance, blood flow and drainage, to replace the original terms—vascular, tubular and excretion.

The first segment is shown to represent a small amount of tubular activity, renal blood activity and extrarenal tissue activity. If one used albumin I^{131} the tubular activity could be eliminated and the true height of the first segment ascertained. If one repeated this after unilateral nephrotomy it was shown that the renal bed had an activity which was 90 per cent of the normal side. In this manner it is shown that the first segment actually reflects activity in the extrarenal tissues and does not reflect changes in renal blood flow. Therefore, the term tracer appearance is a more accurate description of the first segment than the old term vascular segment.

The second segment reflects the integration of tracer accumulation in the kidney, its excretion from the renal pelvis and declining radioactivity in the blood. The excretion into the renal pelvis is negligible as is the decay of the isotope. The accumulation in the kidney is a function of renal blood flow because at the dosage level employed, 92 per cent of the iodohippurate I^{131} is cleared with each passage through the kidney. This blood flow segment is depressed in vascular disease, chronic pyelonephritis, nephroptosis with vascular embarrassment and congestive heart failure. Carbon tetrachloride poisoning represents an exception in which the depressed second segment reflects severe tubular damage.

The overriding importance of the third segment is urine drainage from the upper urinary tract.

Renal transit time is measured from the tracer appearance in the kidney to the beginning of the drainage segment and reflects urine flow. Unilateral prolongation of transit time in the absence of mechanical obstruction to urine drainage is one of the hallmarks of renal artery occlusive disease.—*James V. Grief, M.D.*

TORI, GIULIO. La scintigrafia renale. (Renal scintigraphy.) *Radiobiologia, Radioterapia e Fisica Medica*, Jan., 1963, *18*, 3–24. (From: Istituto di Radiologia dell'Università di Bologna and Insegnamento di Fisica Nucleare Applicata Alla Medicina dell'Università di Bologna, Italy.)

The first results of renal scintigraphy obtained in a limited number of cases are presented. The radioactive compound used was neohydrin labelled with Hg^{203}.

The conclusions of the author essentially confirm the experience obtained by previous investigators.—*A. F. Govoni, M.D.*

HINE, GERALD J., FARMELANT, MELVIN H., CARDARELLI, JOHN A., and BURROWS, BELTON A. Four channel magnetic tape recording and digital analysis of radio-hippuran renal function tests in normal subjects. *J. Nuclear Med.*, Sept., 1963, *4*, 371–381. (From: Radioisotope and Medical Services, Boston Veterans Administration Hospital, the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston, Mass.)

A method of data preservation and reproduction using magnetic tape is described. A magnetic tape system was used to preserve the time sequence of pulses from scintillation counters. This set-up was used to study the excretion of I^{131} hippuran in normal subjects. The excretion of the I^{131} hippuran from the kidney areas and other body sites was followed for 100 minutes.

The use of the magnetic tape to store the information from the scintillation counters provided the necessary flexibility for the analysis of the data to an extent not otherwise possible.

The authors conclude that the excretion of I^{131} hippuran from the kidneys and other body sites could be accounted for by four exponential components with half-times of 2, 10, 50 minutes and one of several hours.—*Isaac Reese, M.D.*

PEARMAN, ROBERT O., and MILLER, JERRY B. Choke voiding cystourethrography. *J. Urol.*, Oct., 1963, *90*, 481–488. (From: Department of Surgery, Division of Urology, University of California Medical Center; and the Department of Urology, Veterans Administration Center, Los Angeles, Calif.)

The term "choke voiding" is used to designate increased resistance to the passage of opaque medium through the bladder and urethra. This can be accomplished by a mechanical choke such as pressure on the urethral meatus or by the use of a viscous medium. By either method, the speed but not the dynamics of the urination is slowed, so that a roentgenogram taken during voiding represents a true functional study of the lower urinary tract. The descent of the bladder, funneling of the bladder neck, and size of the vesical opening are readily demonstrated.

The bladder may be filled with radiopaque medium by the intravenous route such as used in excretory urography. When this technique is used, it is well to inject more than the customary amount of radiopaque medium and also to give the patient approximately 600 cc. of water during the roentgenographic procedure, so that diuresis will aid in filling the bladder. Other methods of filling the bladder are by the usual retrograde catheter or a suprapubicly placed catheter.

To obtain a choke voiding cystogram, the authors attach the Brodny penis clamp to the male urethra so that the patient voids through the tube of the Brodny apparatus thus increasing the intraurethral and intravesical pressure necessary for voiding. During the voiding procedure, roentgenograms are made in the usual oblique position and centered over the bladder, urethra, and lower ureters. A second roentgenogram is taken after voiding is complete.

In the female patient, the authors use a mixture of 6 per cent sodium iodide and thixokon in 6–1 proportion to produce a hydrokinetic choke. A special stool is made of balsa wood for these patients and the films are exposed in the anteroposterior or oblique position during voiding.

The authors illustrate their methods with 14 composite figures.—*George W. Chamberlin, M.D.*

NERVOUS SYSTEM

VOGLER, E., and WALCHER, W. Versuche mit einem neuen Kontrastmittel für die subarachnoidale Myelographie. (Investigations with a new contrast medium for subarachnoid myelography.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Oct., 1963, *99*, 493–506. (Address: Prof. Dr. E. Vogler, Zentral-Röntgen-Institut, Landeskrankenhaus, Graz, Austria.)

The advantages and disadvantages of the gaseous, oily and water-soluble contrast media in use, at present or in the past, are discussed. The new contrast medium, designated SH 617 L, is preferred because it can be injected in the lumbar or suboccipital areas without a prior anesthetic. It is harmless (or produces only mild, transitory irritations), absorbable, and provides satisfactory visualization of the entire spinal canal. Its composition is a 20 per cent crystalline suspension of (3-dimethyl aminomethylamino-2, 4, 6, triiodophenyl) proprionic acid ethyl ester in isotonic 5.5 per cent glucose solution. The iodine content is 61.45 per cent and none of the iodine is free or inorganically bound.

This contrast medium was used in 160 examinations of the spinal canal without any untoward reactions. In the study of the lumbar region, 1–5 cc. may be employed with the patient seated or lying down. In examinations of the suboccipital region, 5 cc. is usually injected with the patient seated. Two immediate myelograms, anteroposterior and lateral, suffice for the cervical region. Myelograms in the same views are taken for study of the dorsal region, but exposures are made 3–5 minutes after injection. In 3 to 4 weeks, 50 per cent of the material is absorbed. After 6 to 8 weeks, only faint traces are still present.—*J. Zausner, M.D.*

SKELETAL SYSTEM

MORRIS, JAMES M., SAMILSON, ROBERT L., and CORLEY, CHARLES L. Melorheostosis: review of the literature and report of an interesting case with a nineteen-year follow-up. *J. Bone & Joint Surg.*, Sept., 1963, *45-A*, 1191–1206. (Address: Dr. James M. Morris, University of California Medical Center, San Francisco 22, Calif.)

This article presents a case of melorheostosis with a 19 year period of observation, during which a definite progression of the disease was recorded. Biopsy material demonstrating a progression from vasculitis to vascular obliteration forms the basis for the authors' speculation that impaired oxygen tension to the involved mesenchymal tissues may be a contributing factor in the pathogenesis of this disease.

The authors have made a statistical analysis of the 131 cases of melorheostosis reported in the world's literature.—*John H. Harris, M.D.*

SCOTT, EDWIN P. Infantile cortical hyperostosis: report of an unusual complication. *J. Pediat.*, May, 1963, *62*, 782–785. (From: Department of Pediatrics, University of Louisville School of Medicine and Children's Hospital, Louisville, Ky.)

This article is a case report of infantile cortical hyperostosis with the rare complication of bony fusion of the radius and ulna. This is the fifth such case in the literature.

The patient was first seen at the age of 2½ months at which time he had the hyperostotic changes of Caffey's disease in the mandible and the radius. He was followed periodically and at the age of 9 months there was resolution of the hyperostosis in most of the bones. The right leg was still involved and there were bony bridges between the radius and ulna on the right. The radial head was dislocated forward. When he was last seen, at the age of 4½ years, the bony bridge in the right forearm was still present.—*John L. Gwinn, M.D.*

STONE, DANIEL B., and BONFIGLIO, MICHAEL. Pyogenic vertebral osteomyelitis: a diagnostic pitfall for the internist. *A.M.A. Arch. Int. Med.*, Oct., 1963, *112*, 491–500. (Address: Dr. Daniel B. Stone, Department of Medicine, University Hospitals, Iowa City, Iowa.)

Fifteen patients, aged 39 to 73 years, with pyogenic vertebral osteomyelitis were diagnosed from mid-1956 to mid-1962 at the University of Iowa Hospitals. Five of these patients had diabetes mellitus. Fever was often present, and leukocytosis usually absent. The level of serum globulin was usually raised and the erythrocytic rate always increased. Roentgenologic changes, often appearing belatedly in the form of bone destruction and paraspinal abscess formation, confirmed the diagnosis. Needle aspiration of the vertebral contents usually permitted bacteriologic culture.

The authors emphasize the difficulty in the clinical diagnosis of vertebral osteomyelitis in the adult. Its clinical manifestations are in great contrast to the more easily recognized manifestations of acute osteomyelitis in children. Adequate roentgenologic investigation of backache in middle-aged or elderly patients is indicated, especially when backache is overshadowed by root pain or comes on after skin infections, after urologic or surgical infection or in the diabetic patients.—*J. T. Ling, M.D.*

Bell, Norman H., Gerard, Earl S., and Bartter, Frederic C. Pseudohypoparathyroidism with osteitis fibrosa cystica and impaired absorption of calcium. *J. Clin. Endocrinol. & Metabol.*, Aug., 1963, *23*, 759–772. (From: Clinical Endocrinology Branch, National Heart Institute, National Institutes of Health, Bethesda, Md., and Department of Metabolism, Division of Medicine, Walter Reed Army Institute of Research, Department of Medicine, Walter Reed Army Hospital, Washington, D. C.)

Pseudohypoparathyroidism is a syndrome characterized by hypocalcemia and hyperphosphatemia without retention of nitrogen, in which there is little or no restoration of serum calcium and phosphorus levels to normal with parathyroid extract. Hyperplasia of the parathyroid glands has been reported in 2 pervious cases and the authors report an additional instance in a patient with pseudohypoparathyroidism which was assumed to be the acquired type because the onset of symptoms and bone disease was in the third decade and there were no skeletal abnormalities characteristic of pseudohypoparathyroidism.

Extensive studies on this patient indicated that secondary hyperparathyroidism and osteitis fibrosa cystica were associated with impaired absorption of calcium, and that large doses of vitamin D enhanced the calcium absorption and led to healing of the bone lesions of osteitis fibrosa cystica. This suggested that the gastrointestinal tract of this patient was resistant to vitamin D and since vitamin D is necessary for optimal activity of parathyroid extract, the high urinary calcium, inspite of a low serum calcium, might be due to resistance of renal tubules to vitamin D and hence to endogenous parathyroid hormone. However, renal control of tubular reabsorption of phosphorus is not entirely independent of endogenous parathyroid hormone, as evidenced by a normal type rise in serum phosphorus and fall in urinary phosphorus after calcium infusion in 2 hypoparathyroid patients both before and after treatment with vitamin D.—*Lois Cowan Collins, M.D.*

Costello, J. M., and Dent, C. E. Hypo-hyperparathyroidism. *Arch. Dis. Childhood*, Aug., 1963, *38*, 397–407. (From: Paediatric Department and Medical Unit, University College Hospital, London, England.)

A 13 year old child is described who presented symptoms from hyperparathyroid bone disease (osteitis fibrosa generalisata) simultaneously with symptoms of mild tetany shown to be due to idiopathic hypoparathyroidism.

On treatment with vitamin D alone the bone lesions healed, and her plasma calcium and phosphorus levels became normal. There were no signs of pseudohypoparathyroidism. Thus a paradoxical state of affairs existed and the authors postulate that two hormones are produced by the parathyroid glands, one affecting calcium and phosphorus levels and the other manifesting itself by production of osteitis fibrosa and a rise in plasma alkaline phosphatase.—*Arch H. Hall, M.D.*

Baker, H., Golding, D. N., and Thompson, M. Atypical polyarthritis in psoriatic families. *Brit. M. J.*, Aug. 10, 1963, *2*, 348–352. (Address: Dr. H. Baker, The London Hospital, London, England.)

Differentiation of the arthritis occurring with psoriasis from classical rheumatoid arthritis on the basis of clinical and roentgenographic features is not secure. Most authors accept the picture of erosive arthritis affecting predominantly or exclusively the terminal interphalangeal joints as being peculiar to psoriatic arthritis. Other features, less reliable, are as follows: (1) absence of subcutaneous nodules; (2) severe osteolysis, arthritis mutilans; (3) resorption of tufts of terminal phalanges; (4) asymmetric involvement of metatarsophalangeal joints, frequent bony ankylosis; (5) mushrooming impaction of tapered distal end of phalanx into the splayed opposed articular surface; (6) involvement of interphalangeal joint of hallux with proliferation of base of distal phalanx; (7) sacroiliac involvement, especially with ankylosis; and (8) "sausage digits" (red swollen toes or fingers due to involvement of interphalangeal joints and tendon sheaths).

Tests for rheumatoid factors are negative in the vast majority of patients with psoriasis and arthritis, whereas they are positive in 80 per cent or more of patients with rheumatoid arthritis. It has been established that there is a hereditary component in the etiology of psoriasis, and genetic factors also bear on rheumatoid arthritis. Some cases of sero-negative arthritis also may be familial. A detailed family history was taken from 53 patients with psoriasis and sero-negative polyarthritis. Forty-seven of the 86 relatives "alleged" to have rheumatism presented for examination. Thirty-seven relatives had no significant abnormality. The remaining 10 relatives and relatives of 6 additional patients form the total of 16 who were studied continuously for 2 years, including periodic Rose-Waaler tests. Only 1 relative had definite psoriatic arthritis; 3 had psoriasis and psoriatic arthritis; 4 had probable psoriatic arthritis, only 1 of which had psoriasis; 11 had arthritis indistinguishable from rheumatoid arthritis, but with negative Rose-Waaler tests in 10, and no subcutaneous nodules.

When psoriasis and arthritis occur together, the skin and joint manifestations may vary greatly in both their individual and relative severity. The psoriasis usually, but not always, precedes the arthritis, and it is necessary to examine the skin, scalp, and nails of patients with sero-negative arthritis of undetermined etiology. The recognition of psoriasis has assumed added importance since the introduction of chloroquine and related compounds in the treatment of rheumatoid arthritis, due to the fact that this and other antimalarial drugs commonly aggravate psoriasis.—*Lois Cowan Collins, M.D.*

HARRIS, R. I., and WILEY, J. J. Acquired spondylolysis as a sequel to spine fusion. *J. Bone & Joint Surg.*, Sept., 1963, *45-A*, 1159–1170. (Address: Dr. R. I. Harris, 609 Medical Arts Building, Toronto 5, Ontario, Canada.)

Six cases with reproduction of roentgenograms are presented to demonstrate that spondylolysis may be due to stress or trauma. Each case developed after a spinal fusion had been performed. In 5 cases the acquired lesion affected the upper-most vertebra included in the fusion and the sixth was found in the fifth lumbar vertebra below the interbody fusion between the fourth and fifth lumbar vertebrae. The various theories as to the etiology of spondylolysis and spondylolisthesis are discussed.

The clinical significance of these acquired defects is uncertain. However, it is suggested that this lesion may in some instances explain recurrence of low-back symptoms after spine fusion. The condition is difficult to diagnose because of the belated appearance of the lesion and the difficulty of roentgenographic recognition.—*J. H. Harris, M.D.*

HOWARTH, M. BECKETT. Management of problems of the lumbosacral spine. *J. Bone & Joint Surg.*, Oct., 1963, *45-A*, 1487–1508. (Address: 49 Lake Avenue, Greenwich, Conn.)

Backache is a common cause of disability, and it is usually associated with structural weakness in the lumbosacral region and with faulty use of the back. It is an indication for careful diagnostic history, physical examination, and adequate roentgenograms. Backache of mechanical origin can be relieved in the vast majority of cases by suitable protective measures, by correction of obesity or faulty posture, by appropriate trunk-muscle exercises, and by training in good posture. Backache unrelieved by these treatments, especially if there is a severe structural defect such as spondylolysis, may be relieved by spine fusion.

Sciatica is also a common cause of disability. Severe persistent sciatica is commonly due to protrusion or extrusion of the nucleus pulposus with pressure against the adjacent nerve root, and it may be associated with neurologic signs of nerve-root pressure. If the sciatica is due to mild nerve-root pressure, partial or temporary relief may be obtained by bed rest for 2 or 3 weeks. Severe or persistent sciatica due to extrusion of a nucleus pulposus is best relieved by careful surgical removal of the material causing the pressure.

The author presents a thorough discussion of the various non-surgical methods of treatment of problems of the lumbosacral spine. As regards prophylaxis, he states that backache may usually be prevented by sleeping on a firm bed, by using proper chair and shoes, by the avoidance of obesity, fatigue, and severe strains on the back, by maintaining the muscles of the trunk in good physical condition, and by good posture.

There is an excellent discussion of etiology, symptomatology, roentgenography, and differential diagnosis, with numerous illustrations.—*Douglas S. Kellogg, M.D.*

BOVILL, EDWIN G., JR. Arteriographic visualization of the juxta-epiphyseal vascular bed following epiphyseal separation: a case report. *J. Bone & Joint Surg.*, Sept., 1963, *45-A*, 1260–1262. (From: The San Francisco General Hospital, San Francisco, Calif.)

A case report of a 7 year old girl is presented who sustained an open separation of the right proximal tibial epiphysis. The popliteal artery and vein had been completely transsected. Three months after end to end anastomosis of both vessels and manipulative reduction of the epiphyseal separation right femoral arteriography was performed. This examination demonstrated that the vascular bed was still increased in the region of the epiphyseal plates in all the bones about the knee. The author believes this to be a result of a general increase in vascularity in response to trauma. There was complete lack of filling, however, of the normal vascular bed on the metaphyseal face of the part of the epiphyseal plate traversed by the fracture line.

Repeat right femoral arteriography 29 months after injury did not opacify the juxta-epiphyseal vascular bed in any of the bones. The growth potential of the proximal tibial epiphysis was not altered during the 3½ year follow-up after injury.—*Gerald J. Kurlander, M.D.*

Norman, Alex, and Bullough, Peter. The radiolucent crescent line—an early diagnostic sign of avascular necrosis of the femoral head. *Bull. Hosp. Joint Dis.*, April, 1963, *24*, 99–104. (From: Departments of Radiology and Pathology, Hospital for Joint Diseases, New York, N.Y.)

The authors direct attention to a reliable early roentgenographic finding in avascular necrosis of the femoral head which has been described previously but has received scant attention. This finding is a crescent shaped radiolucency which parallels the subchondral surface of the femoral head. It is visible because a narrow margin of bone is still in place close to the cartilage.

A study of 3 femoral heads removed from patients with avascular necrosis indicates that the crescent-like zone of radiolucency is an area of subchondral separation and not resorption of necrotic bone. The bone underlying the subarticular defect is nonviable.

The frog-lateral view best demonstrates the radiolucency because of the frequency of involvement of the anterolateral margin of the femoral head.—*Gerald J. Kurlander, M.D.*

Swanson, Alfred B., Glessner, James R., Jr., Burdick, Harry W., and Mahaney, Robert C. Seven years' experience with irradiated bone graft material. *Surg., Gynec. & Obst.*, Nov., 1963, *117*, 573–577. (From: Division of Orthopedic Surgery, Blodgett Memorial Hospital, Grand Rapids, Mich.)

The authors report in detail the preparation of the homografts. The above-knee amputation specimens obtained from operations performed for vascular insufficiency, have been the source of the bone. The contraindications for the use of these specimens have been: positive results of serology, a positive past history of jaundice, evidence of carcinoma or the presence of obvious infection in the extremity.

The amputated extremity is prepared for storage with aseptic technique. The condyles of the tibia and femur are cut off from the shafts and denuded of all cartilage, soft tissue, and cortical bone. The remaining cancellous bone is then cut into cubes about ½ inch square. The shaft portions of the bone are stripped of all periosteum and soft tissues. The bone is then placed in sterile jars and stored at −20° C. When several specimens have been so prepared, the bone is then ready for processing with clean, but not necessarily sterile technique.

The cancellous bone is osterized with ice and saline into particles not exceeding 1 mm. in diameter. The cortical shafts are cut by motor saw into strips of various widths and lengths but not exceeding 1.5 cm. in total thickness. The authors state that this thickness is of extreme importance as the clinical trial revealed that 1.5 cm. is the maximum thickness of bone capable of being sterilized by the radiation dosage used. Some of the strips of bone are run through a hand lathe to tap bone screws according to the method of Eicher.

The 3 types of bone—cancellous, cortical strips, and screws—are packaged in separate, pliofilm envelopes 0.04 mm. thick. Each envelope contains 1 screw, 1 or 2 pieces of cortical bone, or 1 teaspoonful of ground bone. Sealing of the envelope is carried out by a simple, handoperated, heat-sealing device. Each envelope containing bone graft material, together with a dated tag and a small glass tube is then placed in a large pliofilm envelope and sealed. The glass tube serves as a gross indicator for irradiation purposes, turning brown on exposure to irradiating dose.

The resulting packages of bone are kept at −20° C. in a conventional deep freeze unit until time for sterilization arrives. The bone is then packed in dry ice and transferred to a Van de Graaff accelerator, which produces a possible beam current of 250 microamperes at 2,000,000 volts, resulting in a 500 watt source of irradiating ionizing energy. The bone is irradiated from each side; it is packed in dry ice during irradiation; after irradiation, still packed in dry ice, it is transferred back to the bank and stored in the freezer at −20° C. until used.

Prior to use, the double sealed package is soaked in compound rust inhibitor, a cold sterilizing compound, for 20 minutes. If any leakage is noted in the outer envelope it is discarded. If not, the outer envelope is opened by the circulating nurse with sterile scissors and the inner package removed by the scrub nurse. Roughly 5 per cent of the packages have been found to leak. Bone is arbitrarily discarded at the end of 1 year if unused. Most of the bone is used within a 6 month period from preparation.

The 3 varieties have been employed in various combinations and for different purposes. Bone screws are used most frequently in spinal fusions, in which they are placed vertically across the facets. In 3 cases of spondylolisthesis, screws were placed across the defect from the lamina to the pedicle of the involved vertebra. Bone screws are also used to help stabilize other fusion masses such as a Lambrinudi triple arthrodesis. Ground bone is rarely used alone. Most often it is used with cortical bone to help contour the bony mass, as in a long spinal fusion.

In a summary, the authors state that they have carried out 368 operative procedures in 300 patients with an infection rate of 1.9 per cent. They do not claim that this type of graft is equal to autogenous bone in osteogenetic superiority, and no claim is made for originality in the process of sterilization.

The authors report that experience has proved the irradiated homograft to be an excellent adjunct in bone graft surgery when homogenous bone is indicated for the following reasons: (1) it is a safe source of bone, no case of infection has been observed to be directly attributable to the graft material used; (2) the bone is readily available; and (3) the mechanism of processing and sterilizing is relatively simple and inexpensive.

With increasing availability of the source of sterilization, the entire process can be recommended for increased use in orthopedic surgery.

The authors describe in great detail their methods of preparing and preserving the bone.—*C. Peter Truog, M.D.*

BLOOD AND LYMPH SYSTEM

DE BAKEY, MICHAEL E. Basic concepts of therapy in arterial disease. *Bull. New York Acad. Med.*, Nov., 1963, *39*, 707–749. (From: The Cora and Webb Mading Department of Surgery, Baylor University College of Medicine, Houston, Texas.)

Throughout the Western World, arterial diseases rank among the worst common ailments of man, accounting for more deaths than all other diseases combined. Great progress has been made in this field with more precise angiographic diagnosis and more effective therapy. The concept has evolved that, regardless of etiology, the lesion in many forms of aortic and arterial disease may well be localized and segmental with a relatively normal and patent arterial bed proximal and distal to the lesion. Because of this segmental nature, many lesions are accessible to surgical correction.

Most arterial diseases may be classified into 2 major categories: aneurysms and occlusive lesions. Lesions may be congenital, acquired or traumatic in origin. From a practical therapeutic aspect, however, the location and extent of the lesion with resultant hemodynamic disturbances assume greater significance than the etiologic factors.

Occlusive diseases are classified according to location: lesions involving the: (1) aortic arch, (2) visceral branches of the abdominal aorta, (3) terminal aorta and major branches, and (4) coronary arteries. The predominant underlying condition in all categories is atherosclerosis. The corrective surgical procedures include thrombo-endarterectomy, excision with graft replacement, bypass graft and patch graft angioplasty. Experience with over 5,000 cases has shown that the seamless, knitted dacron tube is more satisfactory than the previously successful arterial homograft. Good results have been obtained in 80–93 per cent of cases.

Aneurysms are similarly classified by site of origin within: (1) aortic arch, (2) descending thoracic aorta, (3) thoracoabdominal segment, and (4) abdominal aorta distal to the renal arteries. Once formed, aneurysms progress to serious or lethal complications, so that extirpation or obliteration of the lesion is essential. Surgical results are gratifying though operative risk is increased by proximal location, advanced age, rupture and pre-existing heart disease.—*David P. Corbett, M.D.*

LEGER, LUCIEN, CHAPUIS, Y., KLOPPER, P. -J., and LEMAIGRE, G. Syndrome de Cruveilhier-Baumgarten: à propos de 28 observations personnelles. (Cruveilhier-Baumgarten syndrome: report of 28 personal cases.) *Arch. mal. app. digest.*, June, 1963, *52*, 609–634. (From: Clinique chirurgicale de l'Hôpital Cochin, Paris, France.)

Routine splenoportography performed in cases of portal hypertension can easily demonstrate the permeability of an umbilical vein serving as a collateral, even in the absence of the classic parietal venous dilatations. This explains the recent and more frequent recognition of this syndrome.

The distinction between the "disease" and the "syndrome" is still controversial. The syndrome is much more common, and is accompanied by portal hypertension, which often is caused by liver cirrhosis or a precirrhotic state. The lesions are sometimes very minimal and confined to a portal and periportal sclerosis. The "disease" is not a well-defined entity; it is very rare, congenital, and the liver is normal with a persistent, permeable umbilical vein.

In the 28 cases reported, the etiology of cirrhosis was alcoholism in 9 cases, bilharziosis in 3 cases, biliary cirrhosis in 1 case, and was undetermined in the others.

The portal hypertension is responsible for the development of a collateral circulation along the umbilical vein, which has remained permeable, or has recanalized along the para-umbilical veins. This, however, is of little functional value; the splenomanometric pressure is usually high, and frequent gastrointestinal hemorrhages occur (in 16 of the 28 cases).

The insufficient venous drainage is easily explained by the fact that the umbilical venous trunk bifurcates, leading to a capillary system acting as a caput medusae, with concomitant retarded flow; moreover, this system is interposed in the abdominal wall between the portal and caval systems.

The persistent, permeable umbilical vein, more often of a large caliber and easily mobilized, can be used advantageously for an anastomosis with the caval vein. Such an omphalo-caval shunt is less traumatizing than the conventional porto-caval anastomosis, and if a thrombosis should develop, an additional porto-caval or spleno-renal shunt can always be performed.

In the cases where the umbilical vein is of a small caliber, the portocaval anastomosis is preferable.—*H. P. Lévesque, M.D.*

Kraft, Richard O., and Fry, William J. Aneurysms of the celiac artery. *Surg., Gynec. & Obst.*, Nov., 1963, *117*, 563–566. (From: Department of Surgery, University of Michigan, and Veterans Administration Hospital, Ann Arbor, Mich.)

Aneurysms of the celiac artery are rare. The anatomic location of the abnormality and the vague nature of the associated symptoms render preoperative diagnosis difficult.

The authors report 2 cases of aneurysms of the celiac artery which were diagnosed preoperatively by lateral percutaneous translumbar aortography. Both of the patients were successfully operated upon with arterial reconstruction. They state that the symptoms attributed to celiac aneurysm are dominated by those associated with rupture of the aneurysm, probably expanding pulsatile mass, epigastric pain, shock and occasionally jaundice and gastrointestinal hemorrhage. Mild subxiphoid discomfort and audible epigastirc bruit may be early signs with this occult lesion.

Although arteriosclerosis is the most common cause of aneurysms of the celiac axis, some of the lesions have been secondary to trauma, or to infectious processes, including syphilis and tuberculosis. Consequently, youth alone does not exclude this diagnosis. Several of the recorded deaths from ruptured celiac aneurysms have been in patients under the age of 40; indeed, microscopic examination of the lesion removed from the authors' second patient demonstrated a defect in the elastic fibers which suggested a congenital condition.

The authors believe that these are, the thirty-seventh and thirty-eighth cases of reported celiac aneurysms; they are the first such aneurysms to be diagnosed preoperatively and the second and third to be removed successfully. The natural history of these lesions makes excisional therapy mandatory.—*C. Peter Truog, M.D.*

Kay, R. G. Retroperitoneal vasculitis with perivascular fibrosis. *Brit. J. Urol.*, Sept., 1963, *35*, 284–292. (From: Department of Surgery, Hammersmith Hospital, and Postgraduate Medical School of London, England.)

This condition is described as an envelopment of retroperitoneal structures by an unusual plaque of fibrous tissue. In the majority of cases this results in a functional type of postrenal obstruction, but vascular complications are not uncommon. The histologic features are nonspecific. The author notes that 125 cases have been reported in the literature. In 50 per cent of these a hypochromic microcytic anemia was recorded. Hoffman and Trippel regard the sedimentation rate as the only constantly abnormal laboratory finding.

Obstruction of the inferior vena cava by the retroperitoneal fibrous tissue has been reported in 10 patients. The aorta was involved in 2 cases. One of these demonstrated abrupt narrowing just below the origin of the renal arteries. The other had marked compression of the aorta with gangrene of the foot. Obstruction of the spermatic veins with development of a hydrocele has been recorded in 3 instances.

A case report is included. Theories of etiology are discussed, and methods of treatment are considered.—*D. S. Kellogg, M.D.*

GENERAL

Clausen, J., Dyggve, H. V., and Melchior, J. C. Mucopolysaccharidosis: paper electrophoretic and infra-red analysis of the urine in gargoylism and Morquio-Ullrich's disease. *Arch. Dis. Childhood*, Aug., 1963, *38*, 364–374. (From: University Department of Biochemistry, Copenhagen, the State Institution for Mentally Retarded, 'Andersvaenge', Slagelse, and the University Clinic of Paediatrics, Rigshospitalet, Copenhagen, Denmark.)

Urinary excretion of acid mucopolysaccharides of varying composition and amount has been found in a number of rare diseases, mainly affecting connective tissues. Two of these are gargoylism and Morquio-Ullrich's disease, the latter characterized by mental retardation, dwarfism, and skeletal changes.

The authors have compared these two disorders by means of a new combined procedure making use of paper electrophoretic demonstration of mucopolysaccharides followed by isolation and identification of the chemical constitution of each by infra-red spectroscopy. In Morquio-Ullrich's disease chondroitin sulphate B and altered hyaluronic acid were excreted in the urine, but not keratosulphate. In gargoylism chondroitin sulphate B was also excreted.

The authors found that infra-red analysis overcame the difficulties encountered in conventional chemical methods of analysis. One should refer to the original article for specific details of procedure.—*Arch H. Hall, M.D.*

Bowers, Dorrance. Marfan's syndrome: the S. family re-visited. *Canad. M. A. J.*, Aug. 24, 1963, *89*, 337–340. (From: Knox Clinic and Kelowna General Hospital, Kelowna, British Columbia, Canada.)

The occurrence and consequences of affliction with Marfan's syndrome have been studied over a period of 6 years in 6 generations of a large Canadian family in which at least 42 examples of the disease have been found.

Marfan's syndrome is an abiotropic disorder of connective tissue in which premature degeneration of the connective tissues is responsible for serious ocular and cardiovascular complications and shortened life span.

Because there is no definitive treatment available, an educational approach to restriction of childbearing by affected individuals is proposed.—*Lois Cowan Collins, M.D.*

Schick, Alfred O., and Gonzalez, Sergio. Contact radiography. *South M. J.*, Nov., 1963, *56*, 1268–1270. (From: Department of Radiology, Morton F. Plant Hospital, Clearwater, Fla.)

Short distance roentgenography has been known for many years but has been used sparingly, and mainly for roentgenography of the sternum. When using this technique the part to be examined is brought as close to the film as possible. The part is magnified slightly but remains in focus, while more distant structures are magnified much more, so that they will often be out of focus and barely visible.

The technique was found useful in examination of certain facial bones, sternum, shoulder girdle, spine and the thicker parts of all extremities. It can occasionally be used in place of laminagraphy or other specialized procedures.

Because of the short focal-film distance the mas. can be reduced, and since air absorption will be practically eliminated, it is important that at least 2 mm. of aluminum filtration be employed.—*Francis P. Shea, M.D.*

Walther, K. Internationale radiologische Beziehungen USA-Deutschland. (International radiologic relationships USA-Germany.) *Fortschr. a.d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Aug., 1963, *99*, 241–245. (Address: Mühlenstrasse 62, 295 Leer [Ostfriesland], Germany.)

The author, who is currently the (unofficial) historian of German radiology, starts his article by recalling that Lowell Goin devoted his 1956 Carman Lecture to the "position of the roentgenologist," a theme favored by Guido Holzknecht since the beginning of the century. In the author's opinion George Pfahler (whose German origin is undisputed) was the most eminent American roentgen pioneer, a fact acknowledged by his being included among the five persons to whom Schinz dedicated the well-known diagnostic text. One of Pfahler's good friends was Georg Fedor Haenisch (of Hamburg) who delivered —on Pfahler's invitation—the 1931 Caldwell Lecture in Atlantic City.

The influx of American students into German medical schools began around 1870. It went hand in glove with the immigration of German physicians to the USA. As a result, in the 1890s there were about five thousand German-American physicians in this country. Then came the "emancipation" of American medicine, while today we are witnessing—in the author's words—the "American" phase in world medicine.

The author then proceeds to enumerate the personal friendships and the various scientific connections developed over the years. He also lists numerous German-American names in American radiology, such as Gottwald Schwarz, Carl Beck, Walter Cowl, Otto Glasser, Wolfram Fuchs, Robert Machlett, and Willy Baensch (the order is that in which they appear in the article).

This article is a valuable and well-documented contribution to the enduring friendship between German and American radiologists, a friendship which has benefited not only the two countries involved, but also the rest of the world.—*E. R. N. Grigg, M.D.*

RADIATION THERAPY

Sauerbrey, Rolf, and Reinhold, Horst. Zur Strahlentherapie des Magenkarzinoms. (Radiation therapy of gastric carcinoma.) *Strahlentherapie*, June, 1963, *121*, 193–199. (From: Strahleninstitut und Strahlentherapeutische Klinik der Medizinischen Akademie, Magdeburg, Germany.)

Of 139 patients (92 male and 47 female) with *inoperable* gastric carcinoma treated with external radiation (through 2 ventral ports to an approximate tumor dose of 2,000 r): 45 (32.4 per cent) survived 1 year; 18 (12.9 per cent) 2 years; 8 (5.8 per cent) 5 years; and 2 (1.4 per cent) for 10 years. Of 87 patients (45 males and 42 females) with gastric carcinoma similarly treated *postoperatively:* 76 (87.4 per cent) survived 1 year; 51 (58.6 per cent) 2 years; 24 (27.6 per cent) 5 years; and 7 (8 per cent) for 10 years.

Survival time for the postoperative patients was not prolonged by irradiation, but the authors recommend radiation therapy of inoperable gastric carcinoma, and of those tumors known to be incompletely removed at operation. Such therapy brings these patients effective alleviation of symptoms as well as prolongation of survival time.—*Henry G. Moehring, M.D.*

Riches, Sir Eric. Surgery and radiotherapy in urology: the bladder. *J. Urol.*, Oct., 1963, *90*, 339–350. (From: The Middlesex Hospital, London, England.)

Cancer of the urinary bladder occurs in two main forms; one is highly malignant and the other is less so. This difference in behavior is shown by the extent and rapidity of spread of the tumor and by its response to treatment. In general, papillary forms are relatively benign, while solid tumors are usually very malignant.

In this article, the author discusses the use of supervoltage radiation therapy as a method of treatment for bladder carcinoma. This type of therapy can be combined with surgery and has been employed mainly for the more serious solid infiltrating tumors. The results of cystectomy without irradiation for solid tumors of the bladder show 9 per cent 5 year survival. The results of supervoltage therapy alone are disappointing although they show 18 per cent 5 year survival. Of 113 patients treated by a full course of radiation therapy, which consisted of 6,700 rads, 22 are still alive and 11 are tumor-free.

The worse complications of supervoltage radiation therapy are telangiectasis with serious bleeding and radionecrosis of the bladder or adjacent bowel. Total or radical cystectomy has been done in 12 patients after supervoltage radiation therapy. Of these, only 3 are alive. Cystectomy at this time may result in a cavity which will not heal.

Interstitial irradiation remains the most satisfactory method to combine with surgery for localized malignant neoplasms of the bladder. Such interstitial irradiation may be done by means of radon seeds, tantalum wire, or radium needles. The addition of these procedures to local excision is, in the author's experience, of considerable value in improving the end results.

Supervoltage radiation therapy is not a good salvage treatment for the hopeless case. It may be used for palliative purposes. It is recommended that, if supervoltage radiation therapy is to be given, local excision of the tumor and urinary tract diversion be done first. After a limited course of about 3,500 rads, a re-assessment should be made to decide whether to proceed with further irradiation or do a total cystectomy.

Nine tables and 11 figures are included in this article.—*George W. Chamberlin, M.D.*

ECKERT, H., and SMITH, J. P. Malignant lymphoma of the testis. *Brit. M. J.*, Oct. 12, 1963, *2*, 891–894. (From: Christie Hospital and Holt Radium Institute, Manchester, England.)

The authors report 35 cases of primary malignant lymphoma of the testis. The term malignant lymphoma is a collective term for all tumors of lymphoreticular origin. Microscopically, most of the tumors were of the reticulum cell type, 2 were of the lymphocytic type, and 1 was a plasmacytoma.

Thirty-five of 665 patients (5.3 per cent) with testicular tumors registered at the Christie Hospital from 1946 to 1962, were of the malignant lymphoma variety. The mean age of the group was 59.8 years as compared with a mean age of 33 years for the teratomas, and 42.3 years for the seminomas in their series.

Treatment consisted of orchiectomy in all cases, followed by "whole abdomen" deep radiation therapy in 23 cases. The radiation technique was previously reported by Gibb.

The sites of metastases are given in a table with intra-abdominal lymph nodes shown to be the most common (17 cases), followed by the mediastinum (10 cases).

Four patients died from unrelated disease with no evidence of recurrence and 5 are still alive. These cases are reported in detail. In the 26 patients dead of disseminated disease, survival from the first symptoms varied from 4 months to 3½ years (mean 14.7 months).—*D. S. Linton, Jr., M.D.*

VAETH, JEROME M., and LEVITT, SEYMOUR H. Five-year results in the treatment of Wilms' tumor of children. *J. Urol.*, Sept., 1963, *90*, 247–249. (From: Department of Radiology, University of California School of Medicine, San Francisco, Calif.)

Thirty patients with histologically verified Wilms' tumors were evaluated for end results; 14 were males and 16 were females. Seventeen were less than 2 years and 13 more than 2 years of age. It is significant that 13 of the 17, less than 2 years of age, survived, whereas only 3 of 13, more than 2 years of age, survived 5 years. When capsule invasion was present, the prognosis was poor as indicated by the fact that only 6 of 16 so involved survived 5 years. When capsule invasion was absent, 10 of 11 patients survived 5 years. The total 5 year survival rate for all patients was 53.3 per cent.

Preoperative irradiation, nephrectomy, and postoperative irradiation resulted in the best survival rate. Preoperative irradiation consisted of 2,500 r in 3 to 4 weeks delivered to the mid-plane followed in 3 to 4 weeks by transperitoneal nephrectomy. Postoperative irradiation carried out 2 weeks after nephrectomy consisted of 3,000 r in 4 weeks.

The authors include 3 tables and 1 composite survival curve to illustrate their statistics.—*George W. Chamberlin, M.D.*

SAXENA, KRISHNA M., and CRAWFORD, JOHN D. Acromegalic gigantism in an adolescent girl. *J. Pediat.*, May, 1963, *62*, 660–665. (From: Department of Pediatrics, Harvard Medical School, and the Children's Service, Massachusetts General Hospital, Boston, Mass.)

Acromegaly secondary to eosinophilic tumor of the anterior pituitary lobe is an uncommon disorder. This is particularly true in children where gigantism is the characteristic manifestation. The case presented is of a 14 year old girl with features of both gigantism and acromegaly and whose disease seems well controlled by treatment.

The case is reported in detail with rather extensive laboratory findings. Roentgenograms of the skull and fingers demonstrate a ballooned sella turcica, remarkable pneumatization of the paranasal sinuses and tufting of the distal phalanges.

The patient was subjected to estrogen therapy which is known to be effective in slowing linear growth as well as in relieving symptoms. However, since relief was transient, radiation therapy with a dose of 4,000 r, using external high voltage source, was delivered to the pituitary gland. There were no untoward effects of the therapy and a one year follow-up showed control of the disease.—*John L. Gwinn, M.D.*

De Schryver, A., and Van Vaerenbergh, P. M. Observations sur le traitement des tumeurs aux électrons de haute énergie. (Observations on the treatment of tumors with high energy electrons.) *J. belge de radiol.*, 1962, *45*, 704–727. (Address: Dr. A. De Schryver, 8, Kasteelstraat, Gentbrugge, Belgium.)

After briefly outlining the physical and radiobiologic fundamentals of high voltage electron-beam therapy, the clinical experience acquired with the treatment of 319 patients during the last 30 months, is reviewed.

Most of the patients chosen for electron-beam therapy presented skin lesions, recurrences, and tumors known as radioresistant.

From the technical aspect, the authors limit the treatment dose per field to a maximum of 300 r, whatever the size of the field, and insist on a perfect localization of the tumor.

During this short period, they have noticed the absence of skin and general reaction, a better tolerance of normal tissue, and a good tumor response to electrons.—*Étienne Lebel, M.D.*

Ciampelli, E., and Pelù, G. Comportamento della intradermoreazione alla tubercolina nei pazienti affetti da morbo di Hodgkin trattati radiologicamente. (The value of intradermal tuberculin reaction in patients with Hodgkin's disease treated radiologically.) *Radiol. med.*, Aug., 1963, *49*, 683–690. (Address: Dr. E. Ciampelli, Ist. Radiol. Univ., Careggi [Firenze], Italy.)

The immunologic reactions to the intradermal tuberculin test were studied in 47 patients with Hodgkin's disease before, at the end of roentgen therapy, and at a later date, in order to demonstrate any modification as a result of the treatment. Analysed also were the delayed responses, which were compared to the period of survival.

Twenty-four patients showed positive skin tests before roentgen therapy. Of these, 16 in later controls revealed no change in the positivity, while in 8 the skin test became negative. Of the 16 cases in which the skin test remained positive, 12 obtained definite benefit from the treatment, with regression of the local involvement and improvement in the general condition. Four cases, however, showed no benefit whatsoever.

Of the 8 patients who exhibited a change in the skin test from positive to negative, the disease continued to progress very rapidly in 7, and only in 1 case was there a moderate local and general improvement.

Twenty-three patients had negative skin tests before roentgen therapy. Of these, 15 in later controls showed again a negative skin test, while in 8 the skin tests became positive. Of the 15 patients in whom the skin test became negative, 6 showed satisfactory results from the treatment. In the other 9 patients there was no improvement in the local and general conditions. Of the 8 cases in which the skin test became positive, 6 showed a satisfactory result, while in 2 the disease progressed quite rapidly.

In concluding, the authors state that the intradermal tuberculin test done before roentgen therapy does not permit any definite evaluation of the further evolution of the disease. The opposite could be said of the reactions to the skin test after roentgen therapy. From the results obtained it appears that of the patients in whom the tuberculin test became positive after treatment, and of those patients whose test was positive before treatment and did not change after treatment, the over-all results were quite satisfactory in a greater percentage, with improvement of the local and general conditions.—*A. F. Govoni, M.D.*

RADIOISOTOPES

Texter, E. Clinton, Jr., Chejfec, Gregerio, and Cooper, John A. D. The I^{131}-triolein absorption test. I. Effect of the nonradioactive meal on the rate of absorption of radioactive-labeled triolein. *Am. J. Digest. Dis.*, Sept., 1963, *8*, 729–741. (Address: 303 East Chicago Avenue, Chicago 11, Ill.)

The purpose of the authors was to study the effect of the nonradioactive component of the meal on the rate of absorption of I^{131}-triolein. I^{131}-triolein has been widely used to determine fat absorption from the intestinal tract. The indices employed are: peak blood radioactivity levels with summation and averaging of the 4th, 5th and 6th hour blood levels; the 6-hour area under the curve representing the appearance of radioactivity in the venous blood; and the excretion of radioactivity in the stool. The level of blood radioactivity at any time is determined by many factors, such as: rate and amount of absorption; utilization and storage of fat; completeness of the thyroid block for iodine; and rate of gastric emptying.

The I^{131}-triolein meal, devised by Ruffin in 1956, consisted of an emulsion of peanut oil, water and Tween 80 containing I^{131}-triolein. Other test meals have used I^{131}-triolein with olive oil and/or milk with or without ginger ale. Some have used capsules containing I^{131}-triolein. The authors used the following meals in this study: I^{131}-triolein in a standard peanut oil emulsion (peanut oil, water and Tween 80); capsules of I^{131}-triolein with breakfast (milk, toast and jam); capsules of I^{131}-triolein in a half milk and half cream emulsion; and I^{131}-triolein in a 48 per cent peanut oil emulsion.

The radioactivity of the blood samples was determined at 2, 4, 6, and 8 hours following the ingestion of the meal. Fluoroscopy of the stomach was done at 4 hours after ingestion of the meal to determine the degree of gastric retention. The radioactivity in the stools was determined on the 5 day collection.

The rate of absorption of the I^{131}-triolein was found to be influenced by the type of the administered meal. The blood radioactivity levels were highest with milk, less with half milk and half cream, and lowest with peanut oil emulsion. The peanut oil emulsion resulted in a delayed absorption due to nausea and inhibition of antral motor activity. The I^{131}-triolein capsules given with a meal resulted in a more rapid initial phase of absorption. There was a delayed absorption if the I^{131}-triolein was given with a peanut oil emulsion.

The I^{131}-triolein in the milk meal was readily accepted and was thought to be more physiologic than the other meals.—*Charles W. Cooley, M.D.*

Vidinli, Mustafa, Texter, E. Clinton, Jr., and Cooper, John A. D. The I^{131}-triolein absorption test. II. Use of I^{131}-triolein milk emulsion as an index of fat absorption in normal subjects and patients with malabsorption. *Am. J. Digest. Dis.*, Sept., 1963, *8*, 742–762. (Address: 303 East Chicago Avenue, Chicago 11, Ill.)

The authors used I^{131}-oleic acid milk emulsions and I^{131}-triolein milk emulsions with and without pancrelipase to study the fat absorption in normal subjects and patients with malabsorption. The I^{131}-triolein milk emulsion consisted of 240 ml. of milk, 10 ml. of peanut oil containing 30 μc of I^{131}-triolein, 1 ml. of Lugol's solution and 20 gm. of barium sulphate; 10 ml. of oleic acid containing 30 μc of I^{131}-oleic acid was substituted for the triolein in the oleic acid studies. Blood samples were obtained at 3, 5, and 7 hours after the ingestion of the meal. Gastric retention was checked at 4 hours by fluoroscopy. Stools were collected for 72 hours. The results were expressed as percentage of the administered radioactivity present in the calculated total blood volume and in the fecal excretion during the period of collection.

Twenty normal subjects were studied. The normal standards of the control subjects for peak blood radioactivity ranged from 11.90 to 21.67 per cent with a mean of 16.63±2.57 per cent. The low range used to separate the normal from abnormal values was 11.90, which approximates the mean minus 2 S.D. or 11.49 per cent. The fecal radioactivity ranged between 0 and 5.54 per cent. The high range used to separate the normal from the abnormal values was 5.54 per cent, which approximates the mean plus 2 S.D. or 5.38 per cent.

The I^{131}-triolein test was done on 118 patients with various conditions such as: pancreatitis, tumor of the pancreas and biliary tract, postgastrectomy syndrome, postgastrectomy and associated pancreatitis or partial pancreatectomy, regional enteritis, enterocolitis and/or small bowel resection, ulcerative colitis, cirrhosis of the liver, sprue, functional diarrhea and other conditions. The mean blood and fecal radioactivity values differed in a statistically significant manner from the normals in the above conditions except for those with functional diarrhea.

The peak blood and fecal radioactivity agreement was usually good, but when there was a disagreement the blood radioactivity was low in association with normal fecal radioactivity. The authors found that the administration of pancrelipase with I^{131}-triolein was more reliable in the diagnosis of pancreatic steatorrhea than with the I^{131}-oleic milk emulsion.

Most of the criticism of the I^{131}-triolein absorption test concerns the failure at times in detecting mild cases of steatorrhea which can be detected by chemical analysis of the stool. Isotopic methods will continue to be used because of their relative simplicity and the unavailability and expense of fecal fat balance studies.

The use of the I^{131}-triolein milk emulsion has advantages over the other techniques and particularly if major reliance is placed upon fecal rather than blood radioactivity.—*Charles W. Cooley, M.D.*

Rothfeld, B., and Osborne, Donald. Malabsorption syndrome produced by neomycin. *Am. J. Digest. Dis.*, Sept., 1963, *8*, 763–768. (Address: Veterans Administration Hospital, Perry Point, Md.)

The administration of neomycin in large doses produces symptoms similar to those found in idiopathic steatorrhea or primary intestinal malabsorption. The steatorrhea ceases when the neomycin is discontinued.

The authors studied the relationship between steatorrhea produced by neomycin and the steatorrhea of gluten-sensitive steroid-responsible absorption defect in patients with primary intestinal malabsorption. The subjects were psychiatric patients in good general health. They were studied using a 50 μc capsule of I^{131}-glycerol trioleate in a test meal containing vegetable oil, water, sugar and a whole egg. The radioactivity of the blood and feces and the fecal fat content were determined. The base line was determined on a diet containing 100 gm. of fat per day. The tests were repeated after: the administration of high doses of neomycin (12 gr./day for 5 days); the administration of neomycin as above and with a gluten-free diet; and after the administration of neomycin with prednisone.

Neomycin produced steatorrhea in 9 out of 10 patients measured chemically. Only 4 of the 9 showed impairment in blood fat levels, and only 5 of the 9 showed increased radioactivity in the stools. Eight of 10 patients maintained normal stool fat levels when on a gluten-free diet. All developed normal levels of blood-radioactive fat when on a gluten-free diet, but 4 of the 10 showed excessive fat in the stool as measured by the I^{131}-triolein test. The steatorrhea produced following the administration of neomycin with prednisone was approximately half as severe as that seen with neomycin alone.

The I^{131}-triolein measured in blood and feces failed to reflect total fecal fat losses in neomycin-induced steatorrhea.

Neomycin-induced steatorrhea is similar to idiopathic steatorrhea in that it can be prevented by the administration of a gluten-free diet during the time it is given and that the administration of prednisone with neomycin decreases the severity of the neomycin-induced steatorrhea.—*Charles W. Cooley, M.D.*

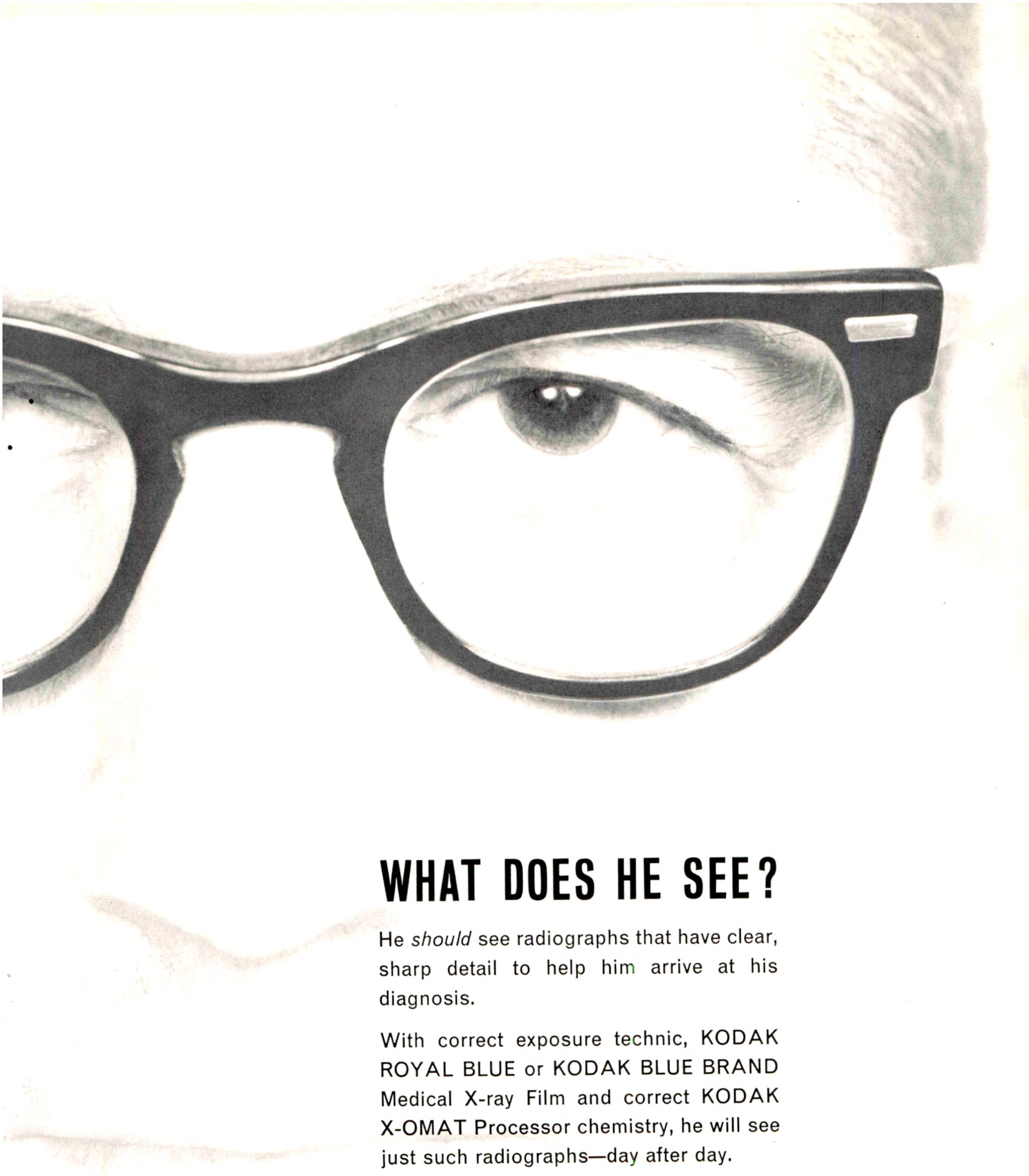
Sodee, D. Bruce. A new scanning isotope, mercury^{197}; a preliminary report. *J. Nuclear Med.*, Sept., 1963, *4*, 335–344. (From: Isotope Section, Radiology Service, Walter Reed General Hospital, Walter Reed Army Medical Center, Washington 12, D. C.)

The author has investigated the use of radioactive mercuric chloride (Hg^{197}) as a scanning agent in hopes of further reducing radiation dosages in this procedure. Hg^{197} has a physical half-life of 2.7 days as compared to 47 days for Hg^{203}. It also decays with 100 per cent gamma emission. Probably because of the attachment of ionic mercury to available sulfhydryl groups, not only the kidneys are visualized by scanning, but also the liver and spleen. Therefore, one diagnostic dose of Hg^{197} will give good evaluation of all three organs, and the procedure is technically much simpler. Radiation to the kidneys is reduced by one-eighth over the Hg^{203} method, and the dose to the spleen is only one-thirtieth of the dose delivered when using the Cr^{51} method.

The author is also evaluating the use of Hg^{197} chloromerodrin for brain and renal scans.—*Richard W. VanBuskirk, M.D.*

Busch, Manfred. Über die Berechnung der Dosisverteilung mit der elektronischen Rechenmaschine bei interstitieller Anwendung von radioaktiven Seeds (ausgeführt am Beispiel der Radiogoldseeds). (The electronic computer and the calculation of dose distribution from interstitial radioactive seeds [illustrated with radioactive gold seeds].) *Strahlentherapie*, Aug., 1963, *121*, 549–555. (From: Strahlenabteilung der Universitäts-Frauenklinik, Freiburg/Brsg., Germany.)

The author describes a program for an electronic computer ("Si-2002") for determining radiation dose distribution from interstitially implanted radioactive gold seeds. The computed doses coincide with the doses measured in a physical reconstruction of the implantation. About 60 minutes are necessary for the computer to print out the dose at 1,600 points with a 15-seed implantation.—*Henry G. Moehring, M.D.*



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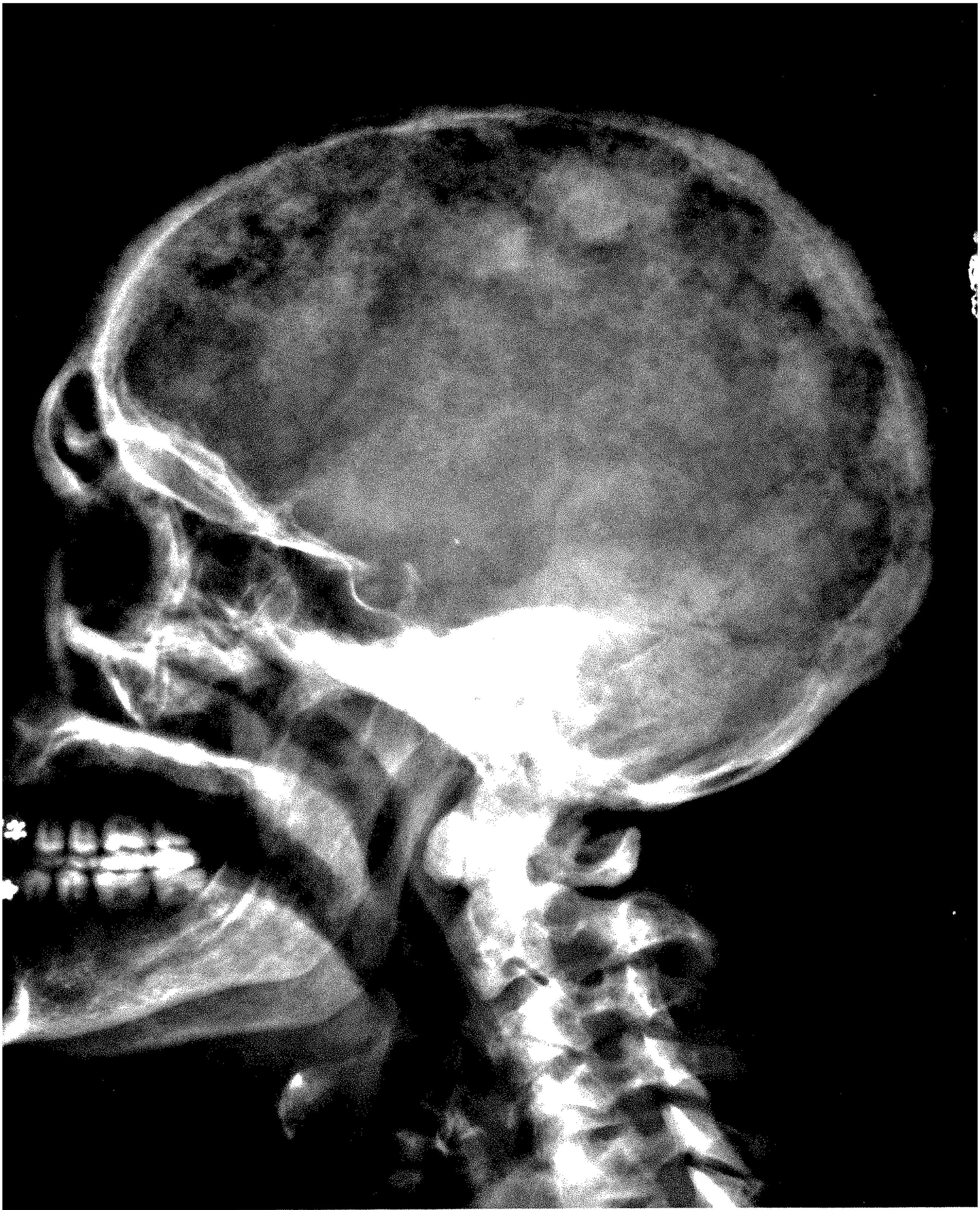

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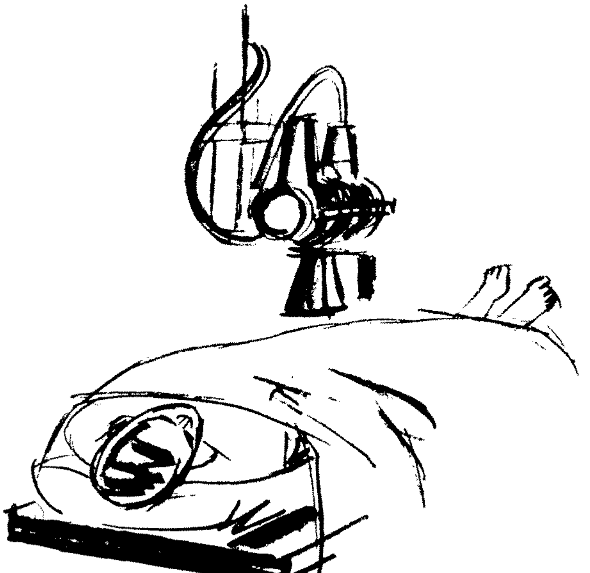

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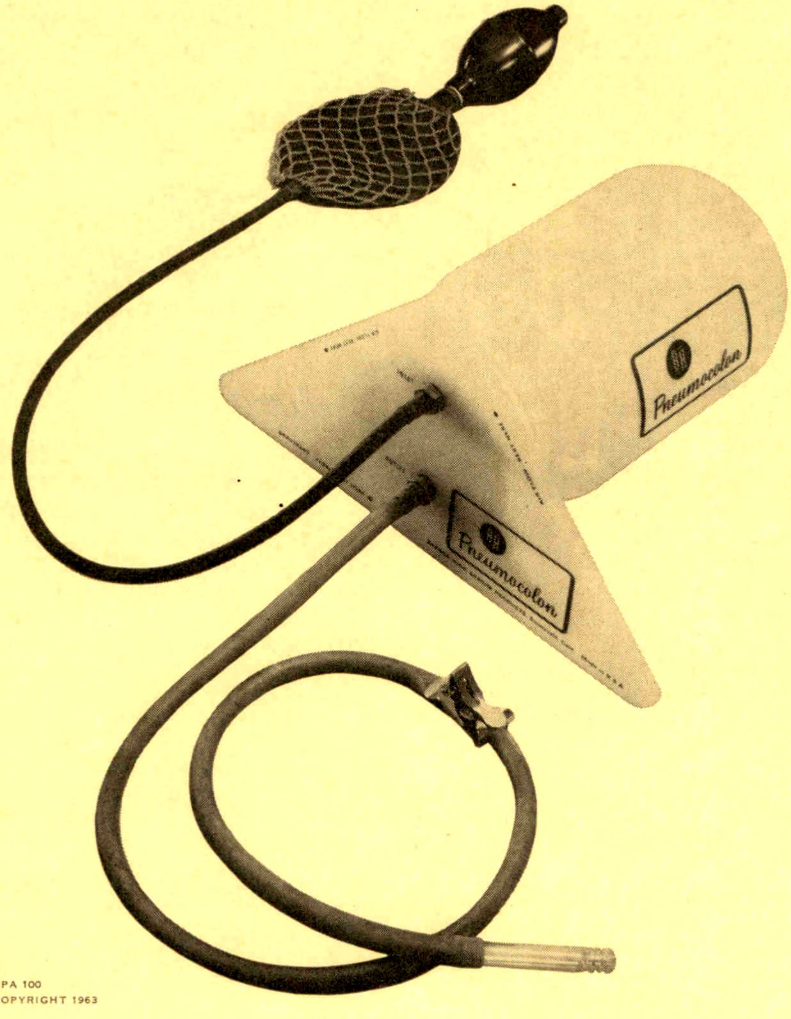

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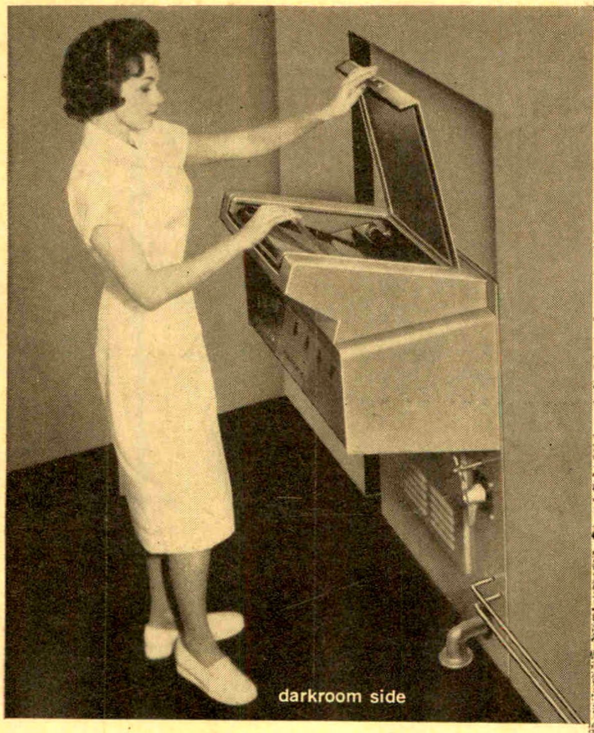
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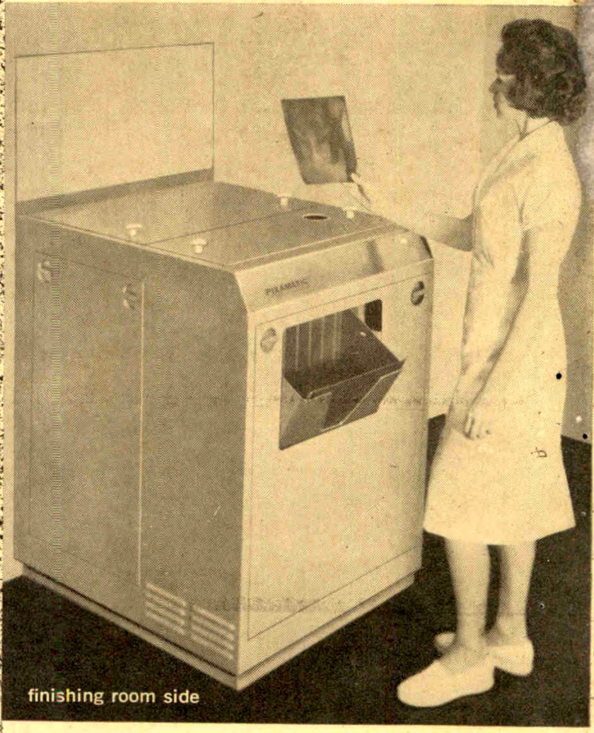
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